THE 2023-2024
JAR GUIDE

UNIVERSITY OF PENNSYLVANIA
DEPARTMENT OF NEUROLOGY

Cover art: Jenna Miller, MD

ACKNOWLEDGMENTS

This guide was originally conceived by former residents Pooja Khatri and Sindhu Ramachadran and significantly revised by Ellen Mowry, David Houghton, and Mike Baer. We are grateful for the contributions of former and current residents, including Mike Baer, Alex Gill, Hannah Machemehl, Jon Rosenberg, Jim Siegler, Colin Ellis, Jamie Adams, Peter Turkeltaub, Heather Moss, Jennifer Graves, Rob Brown, Chris Tjoa, Eric Frechette, Matthew Scharf, Neil Masangkay, Rachel Slotcavage, Judy Jia, and Stephanie Gandelman. Special thanks go to Drs. Ozudogru, Balcer, Bird, Fuller, Galetta, Ganguly, Gonzalez, Herman, Kasner, Levine, Litt, Markowitz, Pruitt, Price, Goldmann-Gross, Aguirre, Lasker, Dalmau and Schmitt for their past and present contributions. Other contributors include former residents and attendings. Contributors to this year's guide in particular are noted in each respective section.

If there are any concerns with the content or formatting for next year, please contact Rachel Thomas.

Good luck with JAR year!
-Rachel and Taha

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LOGISTICS

Information Technology

UPHS help desk: 215-662-7474
QGenda: schedules. https://app.qgenda.com/Account/User/Create
PennPointPlus: calendar, common forms & documents www.neuropenn.com
MEDHUB: calendar, forms, documents, duty hours & evaluations.
https://uphs.medhub.com/index.mh
PennChart: EPIC inpatient and outpatient platform at all sites; Haiku is the mobile app
MEDVIEW: Entire UPHS. Useful for radiology, labs (pathology), EMGs, EEGs.
CareLine: Penn signout program, can be found via UPHS intranet or is integrated in PennChart
SECTRA: Radiology viewing platform (HUP, PAH, PPMC)
PENN IMAGE EXCHAGE: uploading of outside imaging studies
NAVICARE: locate patients within the hospital. **Login = silver9, password = silver9**
Knowledge Link: training modules for ACLS, PennChart, and CITI certification (IRB protocols).
http://knowledgelink.upenn.edu/ (login/pw using PennKey)
Rolodoc: www.pennrolodoc.com ; directory with up to date on call information
Stroke resources: www.pennstroke.org Password: silver9
Neuro Critical Care Resources: **https://www.med.upenn.edu/ncc/secure/**
Penn Neuro Google Drive: login: neuropennresources password: braintrust
Dorsata/PennPathways: houses system pathways for clinical care. https://pathways.dorsata.com/

EPIC ACCESS FROM HOME:
www.pennmedicineaccess.uphs.upenn.edu; will need DuoMobile 2-factor authentication UPHS intranet Applications via Citrix PennChart (will need to have citrix receiver downloaded on your computer)

HOW TO DO A CONSULT

[] find the patient in Epic & add to appropriate list
[] Chart review: focus on HPI, PMH, meds (limit yourself to 10-15 minutes upfront)
- ED note (Medview/PennChart): vitals, orders, written notes, possibly PMH/meds
- recent discharge summaries (PennChart)
- radiology: any prior neuroimaging?
- pathology: todays labs; prior labs
- neurology tab (Medview): prior EEG? EMG?
- PennChart: ever seen neurology? Helpful PCP notes? PMH/med list?

[] see patient for history and exam
[] develop assessment and plan
[] call senior
[] write PennChart/Epic consult note; use template **.neuroadmissionandconsult** and link to consult order (see Neurovascular section for stroke alert logistics!)
[] relay recs to primary team
[] update Carelign signout: HPI, data, meds, A&P, cross-cover

LOGISTICS

HOW TO DO A PRE-ADMIT

1. For Admissions from ED
   a. Search patient in PennChart
   b. Right click patient hit “Assign Team” choose appropriate team
   c. Click “Admissions” tab on left side bar
   d. On new left side bar click “Review PTA Meds” this serves as part of med rec
   e. On new left side bar below “Review PTA meds” click “Admission orders”
      i. Review home meds/Review orders/Reconcile home medications.
      ii. Under “New orders” place appropriate admission order set
      iii. Click Sign/Held- RN will release these orders when patient on the floor
2. For Pre-Admissions (I.E. EMU)
   a. Use Login context “HUP Neurology”
   b. Search patient, click admission encounter and follow above steps

IMAGING STUDIES:

UPHS Studies: SECTRA IDS7 or SECTRA UNIVIEW
Outside Studies uploaded from CD:
- Penn Image Exchange
- Chester County PACS

Uploading to Penn Image Exchange and Epic

(done by the secretary if you’re in clinic, otherwise you do it)

1. Insert CD
2. Click on “PIX Upload” left side-bar EPIC menu (may be under rarely used)
3. Select Destination: “Integration”
3. Click ”Find exams on CD.” Check the studies you want to upload.
4. Upload. The images may last up to 7 days on this temporary server.

If you want radiology to INTERPRET the study:

1. In PENNCHART: Open an “Orders Only” encounter for the patient (if outpatient).
2. Place an order for the type of study you want transferred. Within the order navigator:
   1. Pacemaker/ICD? No
   2. Mettalic Devices? No
   3. Study to be performed at HUP/PERELMAN? YES
   4. If this order is for storage of outside films...: Selectr appropriate option
   5. Status:normal
   6. Class: Ancillary Perfromed
   7. Priority: Routine
   8. Commends: Type “storage of MRI brain dated *** from Penn Image Exchange
3. Have the OSH read faxed to Radiology Image Library (215-349-8448) for comparison. Scans will not be interpreted without an outside read. Call 215-615-5958 with

LOGISTICS

Special Considerations for High-use Medications

INTRAVENOUS IMMUNE GLOBULIN (IVIG)

Immune serum polyvalent IgG made from pooled human plasma from several thousand donors
Many available formulations which differ by stabilizers (type of sugars used), shelf life and storage requirements

LABS PRIOR TO STARTING IVIG

- HIV, hep A, B and C serologies, CBC, LFTs and renal function
- consider checking IgA levels (to avoid IgA deficiency anaphylaxis)
- Any antibodies you want tested for the disease in question, as IVIg may cause false-positive results

DOSING: 2g/kg divided over 5 days (if IVIg naïve, otherwise can consider dosing over 2 days)

PREMEDS: Acetaminophen, diphenhydramine, IV fluids

MONITORING (for chronic IVIg treatment)

- creatinine, CBC (for anemia and neutropenia) and Coomb's test (for hemolysis)

ADVERSE EFFECTS

Mild	**Moderate**	**Severe**
Common	**Less common**	**Rare**
Acute (during infusion)	**Delayed (6 hrs – 1 week)**	
Infusion site pain, swelling	Persistent headache	Anaphylaxis (if IgA deficiency)
Headache	Aseptic meningitis	Kidney injury
Myalgia, arthralgia, back pain	Hemolysis	Thrombo-embolism (MI, stroke, DVT, PE)
Fevers, chills, flushing	Neutropenia	Pulmonary complications
Anxiety	Serum sickness, arthritis	Colitis
Fatigue, malaise	Dermatologic	Blood-borne infections
Nausea, vomiting	complications	
Hypertension, hypotension	Vaccine ineffectiveness	
Tachycardia		

THROMBOTIC EVENTS

In patients with no risk factors, risk is <1%.
If ≥4 of column A risk factors, 10x increase risk of thromboembolism

A. Patient risk factors	**B. Additional patient risk factors**	**C. Product specific risk factors**
Coronary artery disease	Hypercoagulable state	Rate of infusion
Stroke	Indwelling catheter	Dose
Hypertension	Immobilization	Presence of activated clotting factors
Hyperlipidemia	Autoimmune disease	
Diabetes	Hyperviscosity (dehydration,	
Tobacco use	paraprotein, etc)	

Steps to avoid thrombotic events:

- Hydration prior to administration
- Lower osmol preparation (discuss with pharmacy)
- Slower administration
- Prophylaxis: heparin or lovenox
- Avoid immobilization after infusion

LOGISTICS

Protocol after Patient Death

FIRST STEPS
[] prepare yourself before entering the room
[] introduce yourself to family and explain what you will be doing

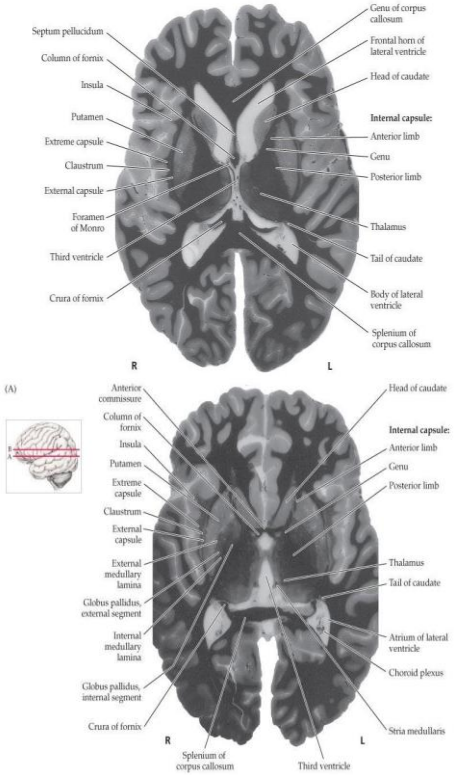
EXAM
[] check patient ID bracelet
[] overall appearance of body
[] response to stimulation
[] pulses: radial, carotid
[] listen for heart sounds
[] look & listen for breath sounds
[] cranial nerve exam

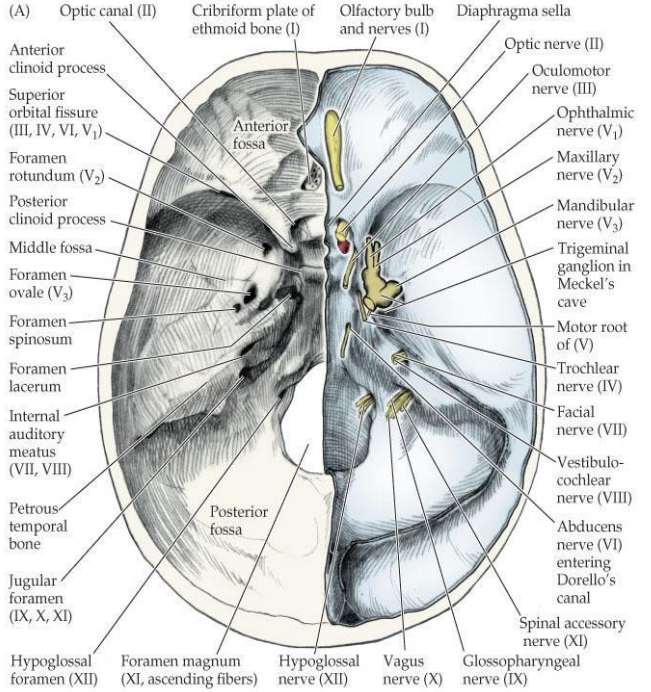
NEXT STEPS: PHONE CALLS & DOCUMENTATION
[] notify attending
[] notify family (if not already present)
[] discuss with family:
(1) ask if they want autopsy (no charge)
-- if yes: they must sign autopsy permission form
-- if via phone: physician and witness both sign permission form
(2) explain that Gift of Life may contact them (we don't discuss organ donation)
(3) ask if they have questions or would like to speak to chaplain
(4) their next step: call funeral director
[] Call Gift Of Life: 1-800-543-6391 (every patient!) ****write down who you speak to!****
[] Death documentation: through "DISCHARGE" tab → select "DISCHARGE AS DECEASED" at the top of the screen.. It guides you step-by-step through the Epic documentation and Electronic Death Registration System (EDRS).

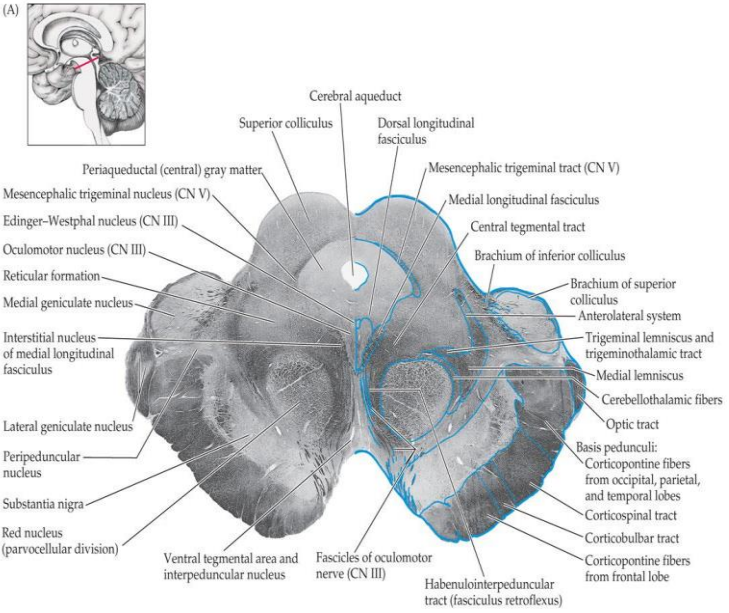
TIPS FOR TELEPHONE NOTIFICATION TO FAMILY
[] never leave news of death on voice mail. Leave specific contact info.
[] identify yourself
[] make sure you are speaking to the appropriate person
[] speak slowly and clearly
[] ask "What have the doctors told you about ___'s condition?"
[] provide a warning shot: "I'm afraid I have some bad news."
[] use clear and direct language: "I'm sorry, ___ has just died."
("Expired", "passed away", or "didn't make it" can be misinterpreted)
[] Allow time for questions

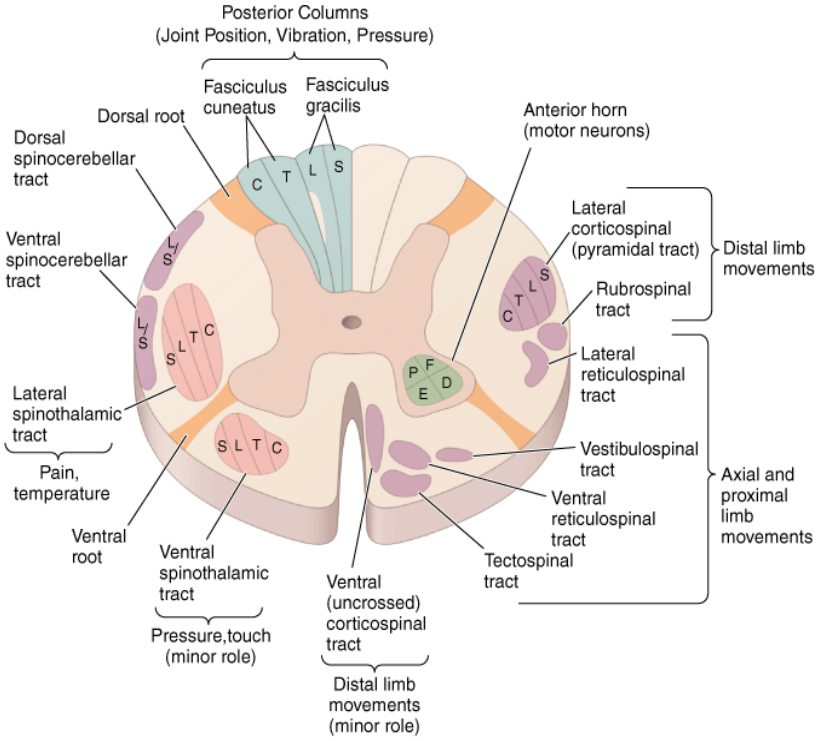
FAQs
[] if family asks about organ donation: we don't discuss that, Gift of Life will call them
[] if family asks "what do we do next?" --> call funeral director
[] if family requests donation of the body: have them sign PA Human Gifts Registry consent form and notify PHGR 215-922-4440.

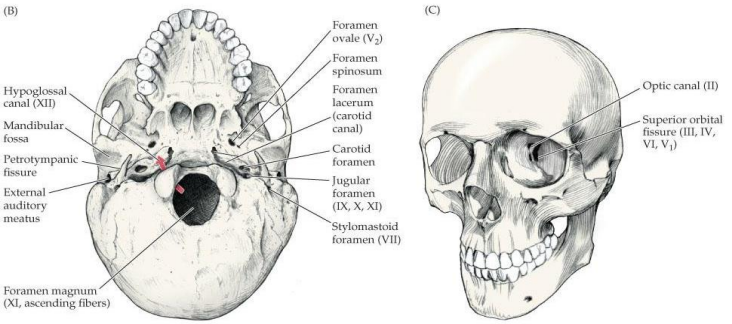
Neuroanatomy




(A)
Optic canal (II)
Cribriform plate of ethmoid bone (I)
Olfactory bulb and nerves (I)
Diaphragma sella
Anterior clinoid process
Superior orbital fissure (III, IV, VI, V1)
Foramen rotundum (V2)
Posterior clinoid process
Middle fossa
Foramen ovale (V3)
Foramen spinosum
Foramen lacerum
Internal auditory meatus (VII, VIII)
Petrous temporal bone
Jugular foramen (IX, X, XI)
Hypoglossal foramen (XII)
Foramen magnum (XI, ascending fibers)
Hypoglossal nerve (XII)
Vagus nerve (X)
Glossopharyngeal nerve (IX)
Spinal accessory nerve (XI)
Anterior fossa
Posterior fossa
Optic nerve (II)
Oculomotor nerve (III)
Ophthalmic nerve (V1)
Maxillary nerve (V2)
Mandibular nerve (V3)
Trigeminal ganglion in Meckel's cave
Motor root of (V)
Trochlear nerve (IV)
Facial nerve (VII)
Vestibulo-cochlear nerve (VIII)
Abducens nerve (VI) entering Dorello's canal


(A)
Cerebral aqueduct
Superior colliculus
Dorsal longitudinal fasciculus
Periaqueductal (central) gray matter
Mesencephalic trigeminal nucleus (CN V)
Edinger–Westphal nucleus (CN III)
Oculomotor nucleus (CN III)
Reticular formation
Medial geniculate nucleus
Interstitial nucleus of medial longitudinal fasciculus
Lateral geniculate nucleus
Peripeduncular nucleus
Substantia nigra
Red nucleus (parvocellular division)
Ventral tegmental area and interpeduncular nucleus
Fascicles of oculomotor nerve (CN III)
Habenulointerpeduncular tract (fasciculus retroflexus)
Mesencephalic trigeminal tract (CN V)
Medial longitudinal fasciculus
Central tegmental tract
Brachium of inferior colliculus
Brachium of superior colliculus
Anterolateral system
Trigeminal lemniscus and trigeminothalamic tract
Medial lemniscus
Cerebellothalamic fibers
Optic tract
Basis pedunculi:
Corticopontine fibers from occipital, parietal, and temporal lobes
Corticospinal tract
Corticobulbar tract
Corticopontine fibers from frontal lobe
(B)
Inferior colliculus (central nucleus)
Cerebral aqueduct
Commissure of inferior colliculus
Lateral lemniscus
Periaqueductal (central) gray matter
Mesencephalic trigeminal nucleus (CN V)
Parabigeminal nucleus
Dorsal raphe nucleus
Trochlear nucleus (CN IV)
Pedunculopontine tegmental nucleus
Median raphe nucleus
Substantia nigra
Interpeduncular nucleus
Pontine nuclei
Pontocerebellar fibers
Brachium of inferior colliculus
Mesencephalic trigeminal tract (CN V)
Fascicles of trochlear nerve (CN IV)
Medial longitudinal fasciculus
Central tegmental tract
Anterolateral system
Tectospinal tract
Trigeminal lemniscus and trigeminothalamic tract
Medial lemniscus
Superior cerebellar peduncle and decussation
Basis pedunculi
Rubrospinal tract





The Neurological Examination

MENTAL STATUS

Arousal state: Alert, Sleepy, Lethargic, Stuporous, Coma. Best to describe stimulation and response (e.g. opens eyes spontaneously, extensor posturing to noxious stimuli)

Attention/Working Memory: serial 7's, spell WORLD backwards, months backwards, count from 20 to 1 listed in decreasing difficulty and sensitivity, digit span (avg 7 forward)

Language: Fluency, repetition, naming, reading, writing, comprehension, ability to follow embedded commands

NEUROANATOMY/NEURO EXAM

Fund of Knowledge: current events, quality of medical Hx
Memory: 3-5 objects at 5 minutes, story retelling, distant memory
Visuospatial: Organization of space (clock drawing, complex figure copy)
Neglect- gaze preference, extinction, line bisection, target elimination
Executive: Organization of knowledge, inhibition, sequencing, perseveration
    Verbal fluency: name animals in 1 minute (>20 normal), f-words in 1 minute (>10 normal)
    Oral trails (A1, B2, 3C....), Luria 3-step (fist, edge, palm) registration and repeat 3 times.
    Go/no go (e.g. raise your hand every time I say a letter, except when I say 'D')

CRANIAL NERVES

I. Olfaction—infrequently tested, check on review of systems for dementia syndromes
II. Visual acuity (pinhole to correct refraction), color vision (red desaturation or color plates)
    Visual fields (cut/neglect)
    Fundus—disc borders/venous pulsations/retina hemorrhage
III. Pupils—size, reactivity to light or near stimuli,
III/IV/VI: Ptosis, eye alignment (exotropia, esotropia, skew), eye movements (saccades, smooth pursuit convergence), nystagmus
V: Face sensation—PP/temp, v1-v3 dist, sensory deficits that split at the midline or endorsement of decreased facial vibratory sensation can point towards functional sensory loss, corneal reflex (nasociliary branch of V → VII)
VII: Face strength— central (spares forehead elevation) vs peripheral (involves forehead elevation), NOTE: CNVII nucleus injury will look peripheral!, hyperacusis, dysgusia, decreased tearing and salivation, check "Ma" and "Ba" for dysarthria
VIII: Hearing— infrequently tested, if unilateral hearing loss, perform Weber, Rinne (see below).
    Vestibular—Oculocephalic reflex (head thrusts), vestibulo-ocular reflex (caloric), Dix-Hallpike, Fukuda march test
X: Palate elevation—Aaaah, uvula position, gag reflex (IX → X), baroreceptor reflex (IX → X), check "ka" for dysarthria, myoclonus (Mollaret's Triangle: red nucleus, dentate nucleus, inferior olive, superior and inferior cerebellar peduncles, central tegmental tract lesion)
XI: Sternocleidomastoid strength/bulk (turns head contralateral)
XII: Tongue—position, bulk, fasciculations (make sure to test with patient's tongue at rest), strength (tongue against tongue depressor), speed, check "La" for dysarthria

Interpretation of Weber & Rinne tests		
	Rinne result	**Weber result**
Normal	Air conducted > bone conducted bilaterally	Midline
Conductive hearing loss	BC > AC in **affected** ear, AC > BC in **unaffected** ear	Lateralizes to **affected** ear
Sensorineural hearing loss	AC > BC in **both** ears	Lateralizes to **unaffected** ear, **away** from affected ear
Mixed hearing loss	BC > AC in **affected** ear, AC > BC in **unaffected** ear	Lateralizes to **unaffected** ear, **away** from affected ear

MOTOR

Bulk (atrophy, fasciculations)
Tone (flaccid, spastic/clasp knife, rigid/lead pipe), abnl mvmt (freq, amp, rest, action, type)
Strength—Drift, satelliting, MRC for isolated muscles (5=normal, 4+, 4, 4-= weak but can resist varying degrees of force, 3=antigravity, 2=movement but not against gravity, 1=flicker of movement, 0=no movement)
Functional tests—heel/toe walking, rise from chair with arms crossed, squat, deep knee bend

CEREBELLAR COORDINATION

Midline/vermis—trunk and saccades; hemispheres—appendicular coordination, Flocculus—gaze holding
Finger-to-Nose, Heel-to-Shin, rhythm testing (RAM), standing with feet together and eyes open

REFLEXES

Muscle Spindle Reflexes—0 to 4+. Interpret the amplitude of response in the context of the amount of force applied. (0=absent, trace=increased force, minimal response, 1+: increased force, normal response, 2+: normal force, normal response, 3+: decreased force, normal or increased response, 4+:clonus)
Jaw jerk (to distinguish cord/brain)
Frontal release (glabellar, rooting, snout, palmomental, grasp)
Hoffman/Babinski

SENSATION

Extremities/trunk/back/perineum—Identify possible pinprick sensory level (can range 2-3 levels above or below site of injury)
Anterolateral system (temp/pp)
Dorsal Columns—vib/discrimination/proprioception, Romberg (stand with feet together and eyes closed), pseudoathetosis
Cortical sensory signs—graphesthesia, extinction, stereoagnosia

GAIT

Base of stance, Stability of stance (provocation), Posture, Initiation of gait, Stepping, Base of gait, Arm swing, Turning rate and balance, tandem walk

THE PEDIATRIC EXAM:

http://library.med.utah.edu/pedineurologicexam/html/home_exam.html

The Coma Examination

EXAMINATION OF THE COMATOSE PATIENT

- Vital signs
  - Cushing's response? (intracranial hypertension)
  - Autonomic hypersensitivity? (NMDAR encephalitis, cervical cord lesion, Bickerstaff's, serotonin syndrome)
  - Breathing over the vent? (intact medullar respiratory center and C4/phrenic nerve)
- Mental Status
  - Key is to describe a *stimulus* and a *response* (e.g. "opens eyes spontaneously", "grimaces to sternal rub"), avoid non-specific wording like "comatose," "obtunded," and "stuporous
  - Glasgow Coma Scale is an effective quantitation method of this and is prognostically useful for many diseases
- Cranial Nerves: afferent → efferent

- Pupillary response: II → III
- Corneal response: V → VII (In ICU check with lash stim → saline → gauze)
- Oculocephalic response: VIII → III, IV, VI
- Cough/gag response: IX → X (In ICU check cough with deep suctioning, gag with ETT)
- Palatal elevation: X
- Primitive reflexes (frontal release signs): rooting, palmomental, glabellar, grasp

- Localization to noxious stimuli/movement
  - Decorticate posturing: elbows/wrists/fingers flexed; legs extended & rotated inward (indicates injury above the red nucleus which favors arm flexion)
  - Decerebrate posturing: extensor posturing of arms and legs (below red nucleus)
  - Triple flexion present? TIP: To distinguish between triple flexion and withdrawal, pinch above the knee – true withdrawal will not move leg into your hand but triple flexion will.
- Reflexes
  - Absent? (spinal shock, acute stroke, GBS or its variants such as Bickerstaff's, peripheral neuropathies)
  - Present? (preserved cord and CNS function)
  - Hyperactive? (post-stroke, post-cord injury, thyrotoxicosis, serotonin syndrome)

Brain Death Examination

** USE REFERENCE FORMS AVAILABLE IN ALL ICU UNITS, **
****DO NOT USE DOWNLOADED MATERIAL ****
** CHECK WITH THE UNIT SECRETARY **

BRAIN DEATH PROTOCOL **Only for ADULTS age 18 or older. See official protocol if age < 18.

Prerequisites:

1. Coma of known cause compatible with brain death. (see below for notes on unknown cause of coma)
2. Exclusion of the confounding conditions:
   a. Severe electrolyte, acid-base, endocrine, or nutritional disturbances (as judged by attending).
   b. Intoxication. Give Narcan if opioids recently on board.
   c. Pharmacological paralysis. Consider twitch monitor if paralytics recently on board.
   d. Temperature must be > 35° C (95° F).
   e. Significant hypotension (as judged by attending)
   e. Injuries to eyes/face that preclude testing

Clinical Examinations:

1. Absence of spontaneous movements, other than spinal reflexes. Absent motor responses to nailbed and supraorbital ridge pressure, other than spinal reflexes (which includes triple flexion).
2. Absence of each of the following brainstem reflexes:
   a. Pupillary light reflex: The pupils should be > 4 mm in diameter and non-reactive
   b. Oculocephalic and oculovestibilar reflexes (cold caloric testing: observe each ear for 1 minute; allow 5 minutes between each side)
   c. Facial motor responses to stimulation: corneal reflex, jaw jerk reflex, facial grimace to pain.
   d. Cough and gag reflexes
3. Apnea Test
   a. no spontaneous breaths during the first two clinical exams

b. Formal apnea testing: off-ventilator apnea test (see Criteria Form for procedure) or on-ventilator apnea test (see Department of Respiratory Care "Testing for a Respiratory Response in the Determination of Brain Death").

WHO PERFORMS THE EXAM

- First exam: Neurology/neurosurgery PGY-2 or higher; Neurocritical Care fellow; or a board-certified neurologist, neurosurgeon, or neurointensivist.
- Second exam: an attending physician who has obtained privileges to determine brain death; a Chief-Resident in Neurosurgery; or a second-year Neurocritical Care Fellow.

TIME INTERVAL BETWEEN EXAMS

- known cause of coma: at least 6 hours.
- unknown cause of coma: at least 24 hours.

UNKNOWN CAUSE OF COMA

- requires a diligent search for the cause of coma before brain death determination. Special care must be taken to perform toxicology studies.
- 24 hours between exams
- confirmatory test required

ANCILLARY TESTS

Ancillary testing is required under the following circumstances:

1. Conditions exist that preclude complete clinical evaluation, including the following:
   a. Facial trauma or deformity that precludes complete clinical evaluation of brainstem reflexes.
   b. Pre-existing pupillary abnormalities (e.g. due to surgery) that preclude papillary exam.
   c. One or both tympanic membranes are ruptured, precluding testing of the oculovestibular reflex
   d. Apnea testing cannot be performed or is indeterminate (ECMO; cardiopulmonary instability).
2. The cause of coma is unknown
3. The examiner deems that levels of sedative drugs might be sufficient to confound clinical assessment.

B. Acceptable ancillary tests in adults:

1. nuclear isotope blood flow scan (preferred).
2. brain-death protocol electroencephalography (EEG).
3. four-vessel catheter cerebral angiogram (if skull is intact).

COGNITIVE

The Cognitive Exam/Anatomy

Special thank you to Dr. Kyra O'Brien for her assistance in editing this section for 2022-2023.

Big picture localization:

- Anterior = action; Posterior = perception
- Left = language; Right = prosody, spatial representation, attention
- Dorsal = where (where is object/self located in space); ventral = what (properties of objects)

6 main cognitive domains:

1. Learning and memory
2. Language
3. Executive function
4. Complex attention
5. Perceptual-motor function
6. Social cognition

Basics of Cognitive Exam

This is a basic outline of how to test the major cognitive domains. *Testing should generally start with an assessment of level of consciousness, orientation, and attention* before diving into the other domains. If a patient is incredibly inattentive then they will not be able to participate in basic tests of memory/language and results from these tests are not valid.

Level of Consciousness: Much of this is assessed based on observation and what the patient is doing during your interaction. *State what you did to elicit a response (ex. yelled, sternal rubbed, etc.) and what their response was (opened eyes, postured, etc.).* Avoid terms like "obtunded" or "stuporous" - just describe what response you saw to what stimuli.

Orientation: assess orientation to location, time, reason for being where they are. Commonly affected with neuro process. Loss of orientation to self is UNLIKELY to be primary neuro!

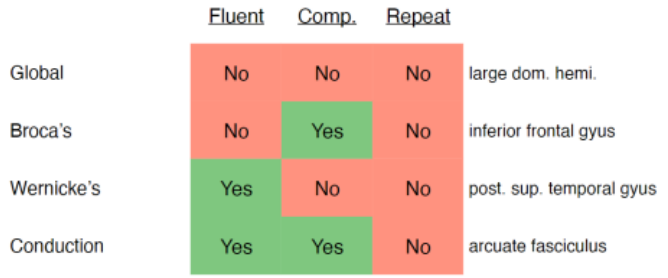
Attention: Specific tests of attention assess if patient can hold on to a particular task/instructions and perform accurately include serial 7's, digit spans, but most often in the inpatient setting you will do months of the year or days of the week backwards.

Language: Can be very localizing. Fluency can be largely gleaned from conversation with patient during history. More focused testing can draw out deficits in comprehension, repetition, and naming.

- Fluency: phrase length, speed, grammar during conversation
- Comprehension: Start from easy to complex. Midline commands, appendicular commands, multi-step commands, embedded clauses (i.e. point to ceiling AFTER pointing to floor)
- Repetition: single words, move to phrases – phrases with physical things to imagine (sunny days) are easier than more abstract phrases (no ifs, ands, or buts)
- Naming: high and low frequency objects, parts of objects harder than the whole object (hands of watch versus watch).

COGNITIVE

Aphasias



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Adapted from Dr. Aguirre's 2022 Behavioral Neurology RITE review lecture

Localization of aphasia types	
Type	**Localizations**
Broca's	Broca's area on inferior frontal gyrus
Transcortical motor	Anterior/superior to Broca's area
Wernicke's	Wider region than Broca's – superior temp. gyrus
Transcortical sensory	Posterior/inferior to Wernicke area
Global	Frontal + temporal regions on dom hemisphere
Transcortical mixed	Adjacent to both Broca/Wernicke areas
Anomic	L temporal cortex
Conduction	Supramarginal gyrus/primary auditory cortex/arcuate fasiculus

From Westover et al. "Pocket Neurology, Second Edition.

Executive function: Classic syndromes → Disorganized (dorsolateral); Disinhibited (orbitofrontal); Akinetic (medial frontal).

- Tests of organization: Luria patterns (alternating between three different hand gestures), oral trails (alternate between letters and numbers)
- Tests of inhibition: Go/No Go, Anti-saccades (hold up both hands, ask patient to NOT look at hand that moves)
- Tests of behavior initiation: mainly based on observation

Memory: with bedside testing you will typically assess episodic memory (hippocampally mediated). Note that memory can be broken down by temporally and categorically

- **Temporal**: Test with 3 word recall.
  - After presentation of stimuli (list of words) an attentive patient will hold and rehearse the information, and then on order of minutes will place information into short term memory. On order of days to months, memories can undergo consolidation (no longer require the hippocampus for retrieval).
  - If a patient is able to recall items with clues, that is more of an executive function (i.e. retrieval) problem than a memory encoding problem.
- **Categorical**: Test by presenting lists of words or short story and asking patient to recall as many words or story features as possible after 5 minute delay.
  - Picture recall (Rey figure) is useful if there is a barrier to language production, or you can point to objects in the room and ask them to remember those items if you do not have a Rey figure with you.
- WHAT (biographical events, words, ideas, concepts) are hippocampally mediated, HOW (skills, emotional conditioning) are non-hippocampal.

Delirium Overview

COGNITIVE

Definition: disturbance in attention and other cognitive domains developing over a short period of time, not better explained by a pre-existing neurocognitive disorder

1st line management is to treat underlying cause, second line below:
o *Hypoactive delirium*: No great management
o *Hyperactive delirium:* 1st line=typical antipsychotics

"DELIRIUMS"	
Drugs	Anticholinergics, antipsychotics, benzos/barbs, serotonergics, stimulants, antihistamines, steroids
Emotions/eyes/ears	
Low PaO2	MI, PE, anemia, COPD
Infection	Urine, resp. tract, CNS
Retention	Stool, urine
Ictal state	Seizure, ICH
Underhydration/ undernutrition	
Metabolic	Glc, Na, BUN, Ca, NH3
Subdural hematoma	

Drug	Qtc prolong	Sedation	Extrapyramidal side effects
Haldol	+++	+	++++
Risperidone	++	+	+++
Olanzapine	+	++	++
Quetiapine	+	+++	+
Aripiprazole	-	+	+

FOR ALL STANDING ANTIPSYCHOTICS
If baseline QTc<460: check EKG for 2 days then stop if stable
If baseline QTc 460-500: check for 3 days (unless titrating dose) then stop
If baseline QTc >500: stop antipsychotic. If benefit outweighs risk, place on tele, daily ekgs, consider decreasing dose by 25 to 50%. D/c other meds that prolong QTc, check daily lytes and EKG

For QTc: always use the Framingham correction as the default Bazett tends to overestimate QTc

HYPERACTIVE DELIRIUM PATHWAY: SEE PENN PATHWAYS (ICON ON INTRANET)

Haldol: if>65 yrs: 0.5-2mg PO/IM/IV. If <65 years 1-5mg PO/IM/IV.
-reassess in 20 minutes, double initial dose(s), maximum 30mg in 24 hours. Maintenance q8-12hrs
Quetiapine: if >65yrs: 12.5-25mg. If <65 years 25-50mg PO q12-q24 hours
Olanzapine: if >65yrs: 2.5-5mg. If <65 years 2.5-10mg PO q12-q24 hours
Risperidone: if >65yrs: 0.25-1mg. If <65 years 1-2 mg PO q12-q24 hours
Aripiprazole: 15mg PO daily
Depakote: 250/250/500, up to 2000-2500 daily. For elderly: consider 125/250, up to to 1500mg daily
-check level (dose by clinical improvement, not therapeutic level)
-taper by 250-500mg daily starting with daytime doses

**** Autoimmune encephalitis: prefer agents with less d2 antagonism (*quetiapine, olanzapine, aripiprazole, depakote*) as these patients are at high risk of extrapyramidal disorders**
**** EPS: benadryl 25mg ivx1, consider benztropine 1-4mg ivx1**
**** NMS: supportive: remove agent, aggressive iv fluids/diuresis, bp support, temp control; consider bromocriptine 5 mg QID vs dantrolene 3-5 mg/kg IV divided 3-4x/d**

Basic Definitions

Dementia

1) Evidence from history and clinical assessment that indicates significant cognitive impairment in at least one of the 6 main cognitive domains.
2) The impairment must be acquired and represent a significant decline from a previous level of functioning
3) Cognitive deficits must interfere with independence in daily activities (listed below)

4) The disturbances are not occurring exclusively during course of delirium
5) The disturbances are not better accounted for by another mental disorder

Mild Cognitive Impairment
A measurable deficit in cognition in at least one domain (see above) that does not lead to an impairment in activities of daily living

Activities of Daily Living:
- Include bathing/showering, personal hygiene, dressing, toilet hygiene, functional mobility (transferring), self-feeding.

Instrumental Activities of Daily Living:
- Include transportation, cleaning/maintaining home, grocery shopping, preparing meals, managing finances, managing medications, using the telephone/managing mail.

Basic workup for cognitive impairment/forgetful presentation

This is a common presentation in resident clinic, and the goal is to determine what is causing these symptoms. Potential etiologies could include, but are not limited to, neurodegenerative processes, reversible causes of dementia, or a multifactorial etiology/do not represent true dementia (pseudodementia in setting of depression/anxiety).
NOTE: Do not underestimate the value of getting collateral from a family member or caregiver! If they cannot be present for the evaluation, it is worth asking patients permission to reach out.

Look for features on history suggestive of a particular cause
- **Alzheimer's Disease:** Short term memory loss and visuospatial function deficits are hallmarks, can also see executive function deficits. Psychiatrically, can see apathy, depression in some.
  - **Imaging/Biomarkers:** Entorhinal cortex/hippocampal atrophy, temporal-parietal atrophy, + amyloid PET, CSF low A-beta, high tau
- **Vascular Dementia**: Impaired executive function, slow processing speed, vascular risk factors +/- stroke history, +/- stepwise progression. Imaging will have cortical/subcortical infarcts, confluent WM disease
- **Lewy Body Dementia**: Parkinsonism, formed visual hallucinations, fluctuating levels of alertness, REM sleep behavior disorder, deficits in attention, visuospatial dysfunction, and executive function. Imaging will have posterior parietal atrophy.
- **FTD**: First symptoms are apathy, poor judgement/impulsiveness, speech/language difficulties, can see apathy, disinhibition, hyperorality, loss of empathy, compulsions. MS exam will have frontal/executive dysfunction and perhaps spare memory early on. Look out for concurrent motor neuron disease (subset w/ FTD-ALS overlap).
- **PSP:** Parkinsonism, postural instability, vertical gaze palsy, axial rigidity, frontal lobe pathology
- **NPH:** Psychomotor slowing, decreased attention, apathy, unstable gait, incontinence
- **CJD:** first symptoms will be dementia, mood, anxiety, visual symptoms, mental status will be variable. Neuro exam will have myoclonus, rigidity, cortical blindness, perhaps parkinsonian features. Imaging will have cortical ribboning and/or pulvinar involvement.
- **Limbic-predominant age associated TDP43 Encephalopathy (aka LATE):** newer diagnosis previously mistaken for AD but only with loss of fluency and short term memory, more common in patients over age 80. Localizes to MTL and severe cases will have hippocampal sclerosis. Think of this if pt clinically has isolated memory/language impairment and severe medial temporal atrophy
- **Pseudodementia from depression:** Psychomotor slowing, poor effort on testing, decreased attention

1) Characterize degree/pattern of impairment with cognitive testing
- **Screening tools** (NOTE: screening tool alone is NOT DIAGNOSTIC OF MCI OR DEMENTIA).

- **Montreal Cognitive Assessment (MoCA)**: Scored on 30-point scale, anything 26 and above is considered normal. *91% sensitivity and 81% specificity for identifying dementia*…freely available at mocatest.org and is *available in multiple languages.*
- **Mini-Mental State Exam (MMSE)**: Scored out of 30. Less frequently used as owned by Psychological Assessment Resources.
- **Saint Louis University Mental Status Examination (SLUMS)**: 30-point scale with better attention to executive function. Free at SLU.edu and has *20 versions in different languages.*
- **Philadelphia Brief Assessment of Cognition (PBAC):** Created by our own Penn team! Assessment of 5 cognitive domains to evaluate cognitive and behavioral impairment, most sensitive for AD and FTD.

When is formal neuropsych testing helpful?

1) Patient has high level of educational or occupational attainment. They might do well on these screening tests and need a better neuropsych battery to detect any cognitive impairment.
2) Someone with history of ADD/ADHD, or significant mood disturbance. It is often difficult to tell how much of the decline is normal cognitive aging on top of ADD versus evidence of a neurodegenerative process. Neuropsych testing can help clarify the cognitive domains that are affected.

2) Screen for depression

Depression can worsen cognition in dementia/MCI or be the main driver of a pseudodementia case. PHQ-2 is simple and if + response can be expanded on. Formal neuropsych testing can also be useful if you are concerned that a low screening test result is from an underlying mood disorder.

3) Send lab testing

AAN recommends screening for Vitamin B12 deficiency (B12 level, CBC, can also send MMA) and hypothyroidism with TSH on all patients. A CMP is also a good idea. RPR/HIV recommended with high clinical suspicion (although in practice we get them on most everyone). Unless there is something fishy (see section below on "Reversible Dementias") you typically won't need to send off other labs.

4) Neuroimaging

Patients presenting with complaint of cognitive impairment and deficits on cognitive testing should get neuroimaging, partly to rule out a treatable cause (subdural hematomas, NPH) and partly to suggest a diagnosis (atrophy patterns, multifocal strokes).

- *MRI w/o contrast is the best modality*. Penn's MRI Alzheimer's protocol includes a coronal T2 that is helpful for looking at hippocampi and medial temporal lobes.
- *FDG-PET is an option if you suspect a neurodegenerative etiology but structural imaging is unremarkable.*

Reversible Dementias

Only a handful of patients will have a reversible cause of their dementia, but the consequences of missing one of these cases is huge. Several red flags can help guide you in workup:

1) Rapid unexplained decline in function
2) Younger than expected age at symptom onset
3) Prominent fluctuations in mental status
4) Acute or chronic high risk exposures (ex. Chronic EtOH use, vitamin deficiencies, other substance use, anticholinergic medications esp. in elderly populations.
5) History of high risk behaviors (ex. Syphilis, HIV)
6) Unexplained/unanticipated findings on Neuro exam

COGNITIVE

A SUMMARY OF THE INPATIENT COGNITIVE IMPAIRMENT WORKUP FOR ACUTE AND CHRONIC CAUSES OF DEMENTIA

DIFFERENTIAL DIAGNOSIS	**DIAGNOSTICS** (1st pass)	**Sometimes useful…** (2nd pass)
Neurodegenerative Alzheimer's disease Fronto-temporal dementia Dementia with Lewy bodies Vascular Dementia PSP, CBD Huntington's disease NPH Hereditary Leukodystrophies Inflammatory/Autoimmune Paraneoplastic: NMDA, VGKC, etc. Hashimoto's encephalitis Primary Angiitis of the CNS ADEM, Tumefactive MS Sarcoidosis Lupus, Sjogren's, RA, Behcet's Epilepsy Subclinical Status Epilepticus Infectious Prion: Creutzfeldt–Jakob Disease Viral: HSV 1>2, VZV, EBV, Rabies, JC (PML) Bacteria: Bartonella, T. whippelii, Mycobacterium tuberculosis Fungal: Cryptococcus Parasites: Toxo, Trypanosoma, Malaria, Amoeba (Naegleria) Syphilis (Neurosyphilis) HIV Vascular VST Bilateral thalamic infarction Chronic Subdural Hematoma Neoplastic Primary CNS lymphoma Primary intravascular lymphoma Lymphomatous or carcinomatous meningitis Also consider: Late effects of brain radiation, gliomatosis cerebri	Blood [] CBC, CMP, LFT's, NH3(?) [] HIV [] Lyme Ag [] Cryptococcal antigen [] ANA, ACE, RF [] TSH, fT4 [] Anti-TPO, anti-thyroglobulin [] Gq-1b antibody [] Autoimmune encephalitis panel [] Mayo paraneoplastic panel [] Copper and ceruloplasmin [] RPR [] B12, MMA, homocysteine CSF [] 14-3-3, RT-Quic (be VERY careful w/ this fluid!) [] check opening pressure, may be ↑↑↑ [] Cells/diff, protein, glucose, gram stain (1 cc's each tube) [] Oligoclonal bands (w/ SPEP), IgG index (5 cc's) [] Cytology & flow cytometry (10 cc's) [] VDRL [] Paraneoplastic panel Urine [] UA, UCx [] UDS Imaging [] MRI brain with/without gad [] EEG/LTM [] CXR [] CT chest/abdomen/pelvis (sarcoid/malignancy w/u) [] PET/CT (malignancy w/u)	Blood [] Smear [] B1 [] SSA/SSB, dsDNA, anti-histone (if drug-induced lupus is considered) [] Heavy metal screen []Copper and ceruloplasmin CSF [] Viral PCR's [] Fungal stain & culture [] Mycobacterial stain & cx [] Tau/a-beta amyloid Urine [] porphobilinogen [] 24-hr copper The ultimate pass if focal lesion and no diagnosis = Biopsy [] Histopathology [] UCSF metagenoimics pathogen detection (CSF)

COGNITIVE

Toxic-metabolic Chasing the Dragon Syndrome Vitamin deficiency: B1 (Wernicke-Korsakoff), E, B12 CO, Lead, Manganese Wilson's disease		

Creutzfeldt-Jakob Disease

Clinical Features/Epi: Most common cause of rapidly progressive dementia in some case series – may account for 20-80% of all rapidly progressive dementia cases (although this may be inflated due to referral bias) Incidence of all prion diseases is 1:1,000,000, increases to 6:1,000,000 if age >65…can be **sporadic, inherited, or infectious** (ex. from transplanted tissue like corneal transplants). Sporadic is the most common subtype by far.

Phenotypes: the end stages of CJD will look similar regardless of initial presentation, with patients exhibiting akinetic mutism. Initial presentations can vary and are outlined in the graphic below.

Diagnosis: Combination of clinical presentation, MRI and EEG findings, and CSF analysis

- **MRI**: shows FLAIR/DWI + in cortex +/- striatum (90% sensitive, 90% specific), usually symmetric but early can be asymmetric. Classic finding is the hockey stick sign, where bilateral pulvinar nuclei show FLAIR/DWI signal. **Enhancement is not typical of CJD**.
- **EEG**: Not as specific as imaging/CSF, but often performed and helps to rule out other causes of rapidly progressive dementia. Typical findings with CJD are period sharp wave complexes, which can be seen in 50% of sporadic CJD patients by the later stages.
- **CSF**: typically do not see pleocytosis but can occur. CSF is obtained to rule out other causes and to perform the tests below:
  1) Detection of proteins (i.e. 14-3-3) in CSF caused by damage of glia and neurons as disease rapidly progresses. **NOTE that detection of these proteins, which include 14-3-3, total tau, S100b, and neuron specific enolase is not specific for CJD!** These simple reflect rapid tissue damage. Over 80% of patients with CJD will have abnormally elevated levels of these proteins.
  2) RT-QuIC (real time quaking induced conversion assay) disrupts prion protein aggregates via shaking and then attempts to induce recombinant prion protein misfolding. *Sensitivity > 90%, Specificity approaches 100%*.

Order 14-3-3 - this automatically reflexes to RT-QuIC

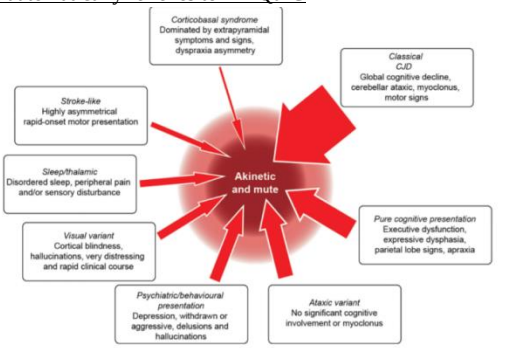


Figure 1 Creutzfeldt-Jakob disease (CJD) clinical features and progression. The boxes describe clinical variants of CJD. The width of each arrow relates to the proportion of cases with the presentation. Patients with CJD become more similar over time, and almost all enter a phase of 'akinetic mutism' before death.

Mild cognitive impairment (MCI)

COGNITIVE

Essentially cognitive impairment (with deficits on cog testing) that doesn't meet criteria for dementia (no demonstrable impact on daily functioning). Can be broken down into different subtypes.
NOTE: there are neurodegenerative and non-neurodegenerative causes of MCI.
Amnestic MCI: present with impaired memory
Non-amnestic MCI: usually isolated issue with non-memory domain (language, visual spatial skills, executive functioning).

Epidemiology
Prevalence by increases by age (estimated in 2018 AAN metanalysis):

- Age 60 to 64 years: 6.7 percent
- Age 65 to 69 years: 8.4 percent
- Age 70 to 74 years: 10.1 percent
- Age 75 to 79 years: 14.8 percent
- Age 80 to 84 years: 25.2 percent

Risk factors – lower educational level, vascular risk factors, history of stroke/heart disease, APOE4 genotype

Progression to Dementia

- Compared to age matched controls, *those with MCI are 3-5x more likely to progress to dementia over next 2-5 years.*
- General rule of thumb= risk of progression is 10% per year (studies range from 5-16%).
- Age is significant risk factor – the older you are with an MCI diagnosis, the more likely you will convert (under 50 it's unlikely that the MCI is pre-dementia).

Treatment

1) **Identify reversible causes**: medication side effects, OSA, depression, B12 deficiency/hypothyroid
2) **Prescribe non-pharm interventions, and modify vascular risk factors:** physical activity, mentally stimulating activity, and socialization can all slow decline, as can a heart healthy diet (the Mediterranean diet, in particular)
3) **Counsel patient on unproven interventions**

- There are no supplements that have been shown to help slow progression (ex. Prevagen, Ginko Biloba, etc.)
- Anti-inflammatory agents like NSAIDs do not have good evidence based (studied due to inflammatory component with AD pathology). Risks here outweigh benefit.

Differences between MCI and normal aging worth noting:

- Language: Vocabulary IMPROVES, naming declines after age 70, verbal fluency (performing word search within a category) also declines with aging. Others in chart:

COGNITIVE

Declines with age	Remains stable with age
Delayed free recall: spontaneous retrieval of information from memory without a cue[24,25] Example: Recalling a list of items to purchase at the grocery store without a cue	Recognition memory: ability to retrieve information when given a cue Example: Correctly giving the details of a story when given yes/no questions
Source memory: knowing the source of the learned information Example: Remembering if you learned a fact because you saw it on television, read it in the newspaper, or heard it from a friend	Temporal order memory: memory for the correct time or sequence of past events Example: Remembering that last Saturday you went to the grocery store after you ate lunch with your friends
Prospective memory: remembering to perform intended actions in the future[26] Example: Remembering to take medicine before going to bed	Procedural memory: memory of how to do things Example: Remembering how to ride a bike

From Harada et al. "Normal Cognitive Aging" Clin Geriatr Med. 2014.

Teasing apart MCI from normal cognitive aging is difficult, as both may present with objective findings on cog testing and opinions may vary between assessors. Best bet is to schedule follow up every 6 months and perform serial testing to look for changes. Patients should always present with collateral when possible. Giving the same advice as listed above for MCI patients is prudent.

Alzheimer's disease (AD)

Clinical features: Neurodegenerative disease marked by accumulation of tau tangles and A-beta plaques...preferentially affects hippocampus then spread through limbic system and neocortex...incidence increases dramatically over the age of 65 (lifetime risk at age 65 is 20% for women, 10% for men)...number of genes contribute to risk, notably APOE genotype – APOE-4 increases risk 3 fold in heterozygotes, 8-12 fold in homozygotes...memory loss typical first symptom, followed by deficits in executive function and visuospatial impairments

Presentation: Typical presentation is short term memory loss initially followed by impairment of any or all other cognitive domains, most commonly executive, visuospatial and language.

General rules of thumb for staging:

- Mild-Moderate: if someone needs help with iADLs but is independent with basic ADLs, they are in the mild-moderate stage,
- Moderate-Severe: When they start having impairments in basic ADLs, they are in the moderate-severe stage.

Typical exam: Procedural memory and motor learning are typically spared early. Memory for facts like vocabulary sometimes spared early (though not always). Category/semantic fluency (such as listing animals or vegetables) is typically impaired (mediated by medial temporal lobe structures).

- For example, this can be seen when someone does WORSE on category/semantic fluency compared to lexical (or phonemic) fluency (which is naming F words, for example). In someone without temporal lobe issues, we usually see people do better on semantic/category fluency.

Imaging findings:

- MRI/CT with atrophy of hippocampus/medial temporal lobes, temporoparietal atrophy, ventricular enlargement. May also see cortical microbleeds indicated co-occurring cerebral amyloid angiopathy (CAA).
- FDG-PET with reduced activation of temporoparietal cortex and posterior cingulate/precuneus

Differential Diagnosis:

- Vascular dementia: Note that there is often significant overlap.
- Dementia with Lewy bodies
- FTD: Primary Progressive Aphasias can be be caused by Tau/TDP pathology or by AD pathology – see AD variants and FTD section

COGNITIVE

Notable AD variants:

- *Posterior cortical atrophy*: Progressive and disproportionate loss of visuospatial functions – often see ophtho first with complaints about reading or finding objects...may develop simultanagnosia and prosopagnosia…will eventually become functionally blind.
- *Logopenic variant PPA*: Progressive decline in language with preserved memory/cognition…involves superior/midtemporal/angular gyrus early…characterized by word finding difficulties, circumlocutions, decreased verbal output and decreased ability to repeat long sentences
- *Limbic predominant age associated TDP43 Encephalopathy (aka LATE)*: see description above.
- *Behavioral variant AD*: early and predominant behavioral symptoms. Looks like bvFTD

Treatment:

1) Slow down disability in mild-moderate AD with acetylcholinesterase inhibitors (AChEIs)

- Who to treat: Those with mild- moderate AD can expect a modest slowing of cognitive and functional decline based on trial data. Does not clearly change long term outcomes. Benefit is more questionable in severe disease but still often used.
- Common side effects: GI upset, loss of appetite, urinary frequency, muscle cramps, vivid dreams, slowing of cardiac conduction (caution in patients with bradycardia).

2) Add on Memantine in moderate-severe AD or if patient can't tolerate AChEIs

- Who to treat: Approved for moderate-severe dementia, though will start in mild-mod AD if cannot tolerate or have a contraindication to an AChEI.
- Common side effects: constipation, dizziness, headache, somnolence.

3) Aducanumab: approved by the FDA for treatment of mild AD, although with unclear clinical benefits

3) Management of behavioral symptoms

- Identify triggers for agitation
- Improve sleep wake cycle w/ exposure to natural bright light
- Encourage regular exercise
- Refer patient/caregiver to social work for support (see "Resources Section" below)
- Can use SSRI's and SNRI's for depression/anxiety
- Avoid TCAs, benzos, and antipsychotics if at all possible (increased mortality for the latter), though can use antipsychotics if they are a danger to themselves or others.

Medication	Mechanism	Recommended Titration[b]
Donepezil	Selective acetylcholinesterase inhibitor	Begin 5 mg daily; increase in 4 weeks to goal 10 mg daily
Galantamine	Acetylcholinesterase inhibitor, allosteric nicotinic receptor modulator	Begin 4 mg 2 times a day; increase by 4 mg per dose increments every 4 weeks to goal of 12 mg 2 times a day
Galantamine ER	Acetylcholinesterase inhibitor, allosteric nicotinic receptor modulator	Begin 8 mg daily; increase by 8 mg/d increments every 4 weeks to goal of 24 mg daily
Rivastigmine oral	Mixed acetylcholinesterase and butyrylcholinesterase inhibitor	Begin 1.5 mg 2 times a day; increase by 1.5 mg per dose increments every 4 weeks to goal of 6 mg 2 times a day
Rivastigmine transdermal patch	Mixed acetylcholinesterase and butyrylcholinesterase inhibitor	Begin 4.6 mg daily; increase in 4 weeks to goal of 9.5 mg daily
Memantine	Noncompetitive glutamate NMDA receptor antagonist	Begin 5 mg daily; increase by 5 mg/d increments every week to goal of 10 mg 2 times a day[c]
Memantine XR	Noncompetitive glutamate NMDA receptor antagonist	Begin 7 mg daily; increase by 7 mg increments every week to goal of 28 mg daily[d]

From Gil D. Rabinovici. "Late Onset Alzheimer Disease." Continuum February 2019.

COGNITIVE

Vascular Cognitive Impairment/Dementia

Clinical features: Primarily executive dysfunction for subcortical cerebrovascular disease, and if they've had a stroke they'll have symptoms from those strokes as well. Imaging will have strokes and WM disease. Can co-occur with AD. Vascular disease contributes to 25-50% of dementia cases, but this has dropped in incidence since the 1970s due to better risk factor control).
Underlying pathology: Vascular risk factors (ex. SVID), cerebral amyloid angiopathy, and genetic (CADASIL/NOTCH) are the 3 biggest risk factors.
Diagnosis/Typical Exam/Imaging: Executive dysfunction with imaging showing cerebrovascular disease +/- strokes as mentioned above. Exam may be somewhat variable depending on distribution of vascular disease.
American Heart Association considers vascular related imaging findings to be sufficient to cause cognitive impairment: Single large/strategically placed infarct, 1-2 large vessel infarcts, >2 lacunar infarcts outside brainstem, extensive white matter lesions.
Differential diagnosis

- AD
- PD/DLB: vascular parkinsonism will typically manifest with bradykinesia in legs more than arms and does not show resting tremor.

Treatment:

- Identify and treat underlying vascular risk factors/stroke mechanisms
- Regular aerobic exercise, at least 3 times per week
- Donepezil has been found to be somewhat beneficial for vascular cognitive impairment
- Screen for depression, treat with SSRIs

Frontotemporal Dementia

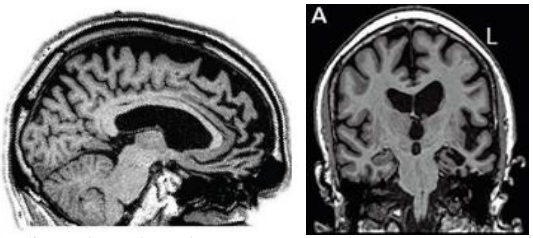
Clinical features: Dementia with selective atrophy of the frontal and/or temporal lobes, pathologically and clinical heterogenous, usually caused by tau/TDP-43 pathology. Peak onset younger than AD (40-60 years). Mainly sporadic but can have a family history. NOTE – FTD refers to clinical syndromes, FTLD (frontotemporal lobar degeneration) refers to underlying pathology (either inclusions staining + for Tau or staining + for TDP). Lots of research currently focusing on linking clinical phenotypes with underlying pathology based on biomarkers.

Subtypes include:

1) **Behavioral variant FTD (bvFTD)**: ½ of FTD cases, see prominent behavioral abnormalities, disinhibition, impulsivity, rigid thinking, impaired judgment, apathy, stereotyped behavior. Imaging with frontal lobe atrophy. In bvFTD you often see right-sided atrophy rather than left (but of course there can be some overlap in phenotypes). **Split between tau/TDP pathology.**
    a) ALS can also have TDP-43. May see overlap between bvFTD and ALS
2) Primary progressive aphasia (PPA) (though note that PPA can be a subtype of FTD or AD). Characterized by gradual onset of language impairment.
    a) Nonfluent variant PPA: effortful production of units of sound – articulatory difficulty most prominent. L frontal lobe atrophy. **Tau>TDP>>AD pathology**.
    b) Semantic variant PPA: impaired single word comprehension/naming with otherwise preserved language functions initially. MRI w/ L anterior temporal atrophy. **TDP>Tau.**
    c) Logopenic variant PPA: Impaired single word retrieval and poor repeitition of longer sentences. **Most often AD pathology.**

Diagnosis: Match clinical presentation and exam with features of bvFTD/PPA's. MRI is useful and can often support the diagnosis based on atrophy patterns (SPECT/PET can also reveal hypometabolism in appropriate structures).
NOTE: **consider referring patient to Dave Irwin for FTD research and to Roy Hamilton for TDCS/TMS research studies if they have aphasia.**

Imaging findings:



Left: bvFTD atrophy pattern (from Seeley. "Behavioral Variant Frontotemporal Dementia." Continuum February 2019). Right: L temporal atrophy in semantic variant PPA (from Botha and Josephs. "Primary Progressive Aphasias and Apraxia of Speech." Continuum February 2019.)

Treatment: Unfortunately there is no disease modifying therapy currently.

- AChEIs are not effective **and can worsen behaviors in bvFTD**.
- SSRIs can help with disinhibition, anxiety, impulsivity and eating disorders based on small studies.
- Antipsychotics are a last resort and can lead to drug induced parkinsonism. However, similar to AD, use if patient is a danger to themselves or others and counsel them that there is black box warning.
- Speech therapy for PPAs
- Ensure that caregivers have adequate support, very emotionally/physically taxing

Normal Pressure Hydrocephalus

Clinical features: Pathologically enlarged ventricles with normal OP on LP (form of communicating hydrocephalus). Classic triad is 1) *gait disturbance* (magnetic, glue-footed gait, difficulty turning, postural instability) 2) *urinary incontinence* (initially w/ urgency and frequency, later with full blown incontinence 3) *dementia* (evolves over years, usually after onset of gait issues, decreased attention and concentration, apathy).

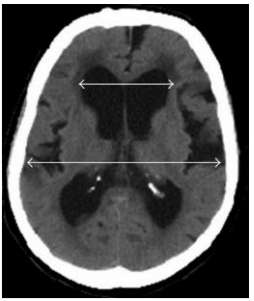
Pathophysiology: unclear cause, may be related to 1) impaired cerebrospinal fluid absorption slowly leading to compensatory ventricular volume increase 2) increased central venous pressure due to incompetence of jugular valves 3) chronic periventricular ischemia leading to increased compliance of ventricular wall and enlargement of ventricles. *All can lead to damage of periventricular white matter and corona radiata, leading to clinical triad*

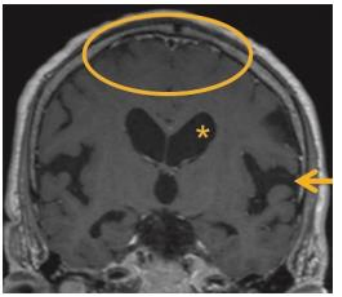
Diagnosis: In practice can be hard to diagnose, as hallmark findings are common in older population for other reasons and ventricles naturally enlarge with age.

1) **Imaging:** MRI will show enlarged ventricles, may see transependymal flow (high signal abnormality around ventricles) or disproportionately enlarged subarachnoid space hydrocephalus (DESH; see pic below). If you suspect NPH based on imaging and symptoms, you should do large volume tap.
2) <u>High volume LP with 25 foot walking test before and after</u>: outside of LP rooms there are marks denoting 25 feet. Have patient walk and record with phone so you have a record. Remove 30-40 cc, send for basic studies. Let the patient rest for a bit, then in 30 minutes record another walk test. Compare the times. Also can make an estimate of the number of steps required to turn around. Improvement is suggestive (PPV of 90-100%, but low NPV). Some patients will improve at home in the days after LP, so typically for the first week after LP, we ask families to monitor gait and cognition for improvement.

<u>NOTE</u>: In cases where the patient has severe dementia and can't walk at all, would be reasonable not to recommend LP.

Imaging findings:





Left demonstrates the Evans index (max. ventricular width in frontal horns divided by largest distance between inner tables of skull. > 0.3 is suggestive of NPH.). Right shows DESH with arrow and high tight convexity with circle. From Graff-Radford and Jones. "Normal Pressure Hydrocephalus." Continuum February 2019.

Treatment: who do you send to NSGY for a shunt?

General rule: If a patient responds to LP, refer to neurosurgery.

- Big picture: shunting works best if you catch NPH early and gait disorder is the most prominent symptom. Once you get at least moderate dementia the cat is out of the bag!

Predictors of improvement after shunting for normal pressure hydrocephalus

Favorable indicators*
Early appearance of gait disorder
Gait disorder most prominent symptom
Shorter duration of symptoms (<6 months)
Identified etiology of NPH
Clinical response to CSF removal (tap test, lumbar drain)
Unfavorable indicators*
Early appearance of dementia
Moderate to severe dementia
Dementia present for more than two years
Gait disorder absent or appearing after dementia
Alcoholism
MRI findings:
▪ Marked white matter disease
▪ Diffuse sulcal enlargement
▪ Medial temporal atrophy

From Radford et al. "Normal Pressure Hydrocephalus." UpToDate.

Cortical Basal Degeneration

See Movement Disorders section

Dementia with Lewy Bodies:

See Movement Disorders section

Driving and Cognitive Impairment

- NJ, PA, and DE have laws requiring doctors to report potentially unsafe drivers
- Criteria (for PA) include: visual acuity, seizures, cognitive impairments, inattentiveness, excessive aggressiveness/disregard for safety of others (amongst other non-neuro criteria)
- In terms of cognition:
  - MCI: studies are mixed about the impact of MCI on driving safety. These patients can benefit from limiting driving to familiar routes and a driving safety evaluation can be

considered. Legally these patients do not need to be reported (unless there are significant concerns from family -- **when in doubt report**!).

- Mod-Severe dementia: Need to legally report. These patients should stop driving.

Another way to think about this: Executive dysfunction and visuospatial dysfunction are two concerning things when it comes to driving. **At the Penn Memory Center, the approach is**: recommend a formal driving evaluation at a rehab center (social work can help make the referral). If they don't want to get it done and insist that they will keep driving, and they have a dementia level of impairment, you should then report them. If they have MCI, use your clinical judgment (amnestic MCI is less concerning for driving than dysexecutive MCI, so for dysexecutive would recommend the driving evaluation but do not need to necessarily report unless there is a family concern or they've had accidents). Also ask pts to stop driving until they have the evaluation done - if they say no, report.

Resources

Penn Memory Center Programs https://pennmemorycenter.org/programs-services/

- Offers caregiver classes, exercise programs, "Memory Café's," cog fitness programs. As a non-PMC patient, pts can sign up for classes and memory cafes, and other events, but not psychotherapy. Contact info for each program is listed on the website.

When to refer to Penn Memory Center:

- If significant social issues that require intensive social work support
- If the patient is interested in research opportunities.

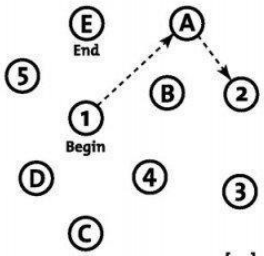
When to refer to social work: patient needs a driving evaluation, patient distressed over diagnosis and needs support, caregiver burden, financial assistance for home care, identifying assisted living facilities or adult day care, identifying transport services (for those who can no longer drive), meal services for those who can't cook for themselves.

COGNITIVE

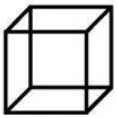
MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE



Copy cube



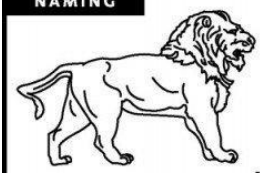
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

POINTS __/5

NAMING



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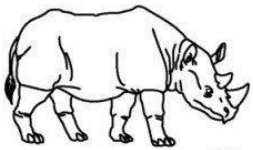

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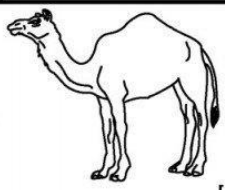


[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words)

__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

DELAYED RECALL

	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org

Normal ≥ 26 / 30

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

PHILADELPHIA BRIEF ASSESSMENT OF COGNITION (PBAC) v 4.0

Name _____
Education _____ Age _____
Dx _____
Date _____

VERBAL LEARNING	Trial 1	Trial 2	Trial 3
Shoe			
Book			
Chair			
Apple			
Cup			
Lake			

LETTER FLUENCY (1/2 pt) /8			
15 S	30s	45s	60s

RECALL (1pt) /6	RECOGNITION (1/2pt) /3	
	Shoe	Hat
	Book	Paper
	Chair	Couch
	Apple	Peach
	Cup	Plate
	Lake	Mountain

ORAL READING (1/2pt) /2			
Choir		Pint	
Yacht		Cough	

NAMING (1pt) /6		SPEECH (-1/2pt) /-4	
Saw		Word-finding pauses	
Mushroom		Circumlocutory	
Camel		Paraphasic - semantic	
Tongs		Paraphasic - phonol	
Asparagus		Agrammatic	
Pelican		Effortful	
		Dysarthria	
		Discourse	

DIGITS (1/2 pt) /3		DIGITS BACK (1pt) /6	
582		85	
6493		463	
42751		5174	
619483		19286	
5718264		536417	
85927416		8179364	

REPETITION (1pt) /1	
No ifs ands or buts	

REY FIG (1pt)	COPY /12	RECALL /12
Large rectangle		
Left cross		
Upper triangle		
Inside diagonals		
Circle		
Up triangle line		
Inside vertical		
3 lines		
Right triangle		
Inside horizontal		
Diamond		
Right triangle line		

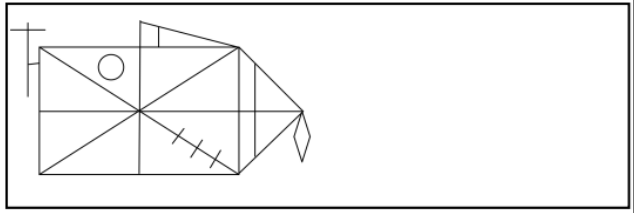
BEHAVIOR / PERSONALITY /18			
No imp (3pt)	Mild (2pt)	Moderate (1pt)	Severe (0pt)
Apathy ___/3	prompts for volitional activities	prompts for self-care	physical assistance
Disinhibit ___/3	mild ↓ manners, impulsivity	inapprop gestures / remarks	grossly inappropria te
Agitation ___/3	mild anxiety/ irritability	disruptive, not harmful	explosive, threatening physical
Ritual/ OCD ___/3	repetitive not disruptive	disruptive, can be redirected	cannot be redirected
Empathy ___/3	inconsiderate / thoughtless	overt disregard for feelings	total disregard for physical pain
Self-Insight ___/3	diminished concern	minimal awareness	complete denial

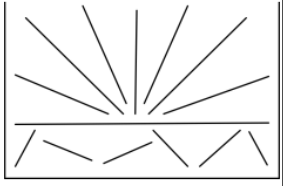
SENTENCE (1pt) /3	
Content	
Grammar	
Spelling	

SEMANTIC (1/2p /3	
Animal	
Vegetable	
Tool	

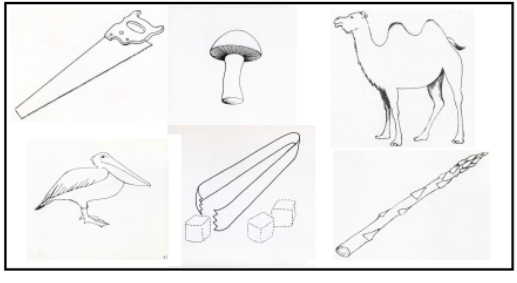
LINE ORIENT (1pt) /6	

TOTAL SCORES	
MMSE	/30
Memory	/18
Language	/18
Vis-Percep	/18
Executive	/12
Total	/93





Rey Recall



CHOIR YACHT PINT COUGH

Sentence:

EPILEPSY

Basic definitions

Epilepsy: Per the International League Against Epilepsy, two unprovoked seizures occurring more than 24 hours apart OR one unprovoked seizure with increased risk of further seizures (greater than 60% recurrence risk over ten years) as may be seen with a structural lesion, CNS infection, TBI, abnormal EEG.

> Side Note: "International League Against Epilepsy" was the original name of the Justice League, but it didn't stick.

There are two seizure pathways now in use across the system- "First Seizure of Life" and "Breakthrough Seizure." Please refer ED providers to these ordersets and utilize these pathways in Dorsata/PennPathways.

Types of Seizures -- classified by onset, awareness, clinical manifestation

-Onset

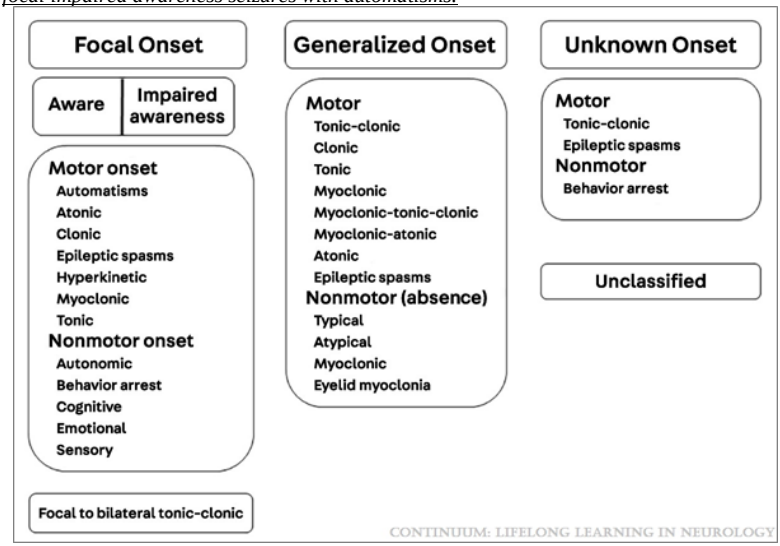
- **Focal** (start in one specific lateralized area in brain)
- **Generalized** (rapidly engage bilaterally distributed networks)

-Awareness

- **Retained** (patient can remember and describe events)
- **Altered/impaired** (period of time during seizure that patient is unaware of surroundings/events)

-Features present after onset – automatisms, clonic movements, myoclonus etc

Example: A patient's seizures start with staring off, followed by lip smacking, then postictal confusion. The patient can feel the seizures coming on but blanks out during. You would say these are *focal impaired awareness seizures with automatisms.*



From Alison Pack, "Epilepsy Overview and Revised Classification of Seizures and Epilepsy." Continuum April 2019.

Select Generalized Epilepsy Syndromes						
Syndrome	Onset age	Inheritance	Seizure types	EEG	Prognosis	Treat

Childhood Absence Epilepsy (CAE)	6-8 yrs	AD, FHx is 15-40%	-Brief episodes of behavior arrest/staring (absence) -Automatisms, clonic jerks, incontinence, loss of tone - Can have up to 100 sz/day, absence status - GTC in 20%	Ictal: bilateral 3 hz spike-wave, activated with hyperventilation Interictal: normal	>65% outgrow epilepsy. Increased risk of ADHD. - Can worsen with CBZ	ETX, VPA, LGT, ZNS, Benzos
Juvenile Absence Epilepsy (JAE)	7-16 yrs	AD	-Simple absence szs -GTC in 80% -Myoclonic jerks in 15%	Ictal: bilateral 3 hz spike-wave. Activated with hypervent and photic riving. Interictal: Can be normal	Most kids don't outgrow. GTCs/Myoclonic szs predict progression to JME. Can worsen with CBZ	VPA, LTG, ZNS
Juvenile Myoclonic Epilepsy (JME)	12-18 yrs	FHX in 40%	-Myoclonic sz, mainly in morning -GTC in 90% -Absence in 1/3 -Precipitated by sleep dep, EtOH (college!)	Ictal: bilateral high voltage 10-16 hz polyspikes followed by 1-3 hz slow waves, activated by photic stim. Interictal: 3.5-6 hz multi-spike wave complexes	Treatment into adulthood is necessary, 14-20% may eventually remit Can worsen with CBZ	VPA, LTG, LEV, TPM ZNS

Adapted from CHOP Neurology Resident Handbook

Typical Features of Focal Seizures by Region of Onset	
Temporal lobe	**Frontal Lobe**
Mesial TL: Aura (epigastric, psychic, affective, olfactory), impaired consciousness, fixed stare, early oroalimentary automatisms, limb automatisms (bilateral or ipsi to focus), dystonic posturing, postictal confusion and amnesia. Most commonly caused by MTS. *Lateral TL*: Aura, eg. Hallucinations (auditory, complex perceptual or experimental), language dysfunction, late oroalimentary automatisms = spread to mesial TL	Brief, often in clusters; little or no postical confusion; rapid generalization; motor sx (clonic, tonic, postural); hyperkinetic complex or bizarre automatisms (e.g. bicycling); sexual automatisms; frequent falls; nocturnal predominance. Uncontrolled laughter can occur with frontal lobe seizures, but is classically associated with hypothalamic hamartomas (gelastic seizures with "mirthless laughter").
Occipital Lobe	**Parietal Lobe**
Elementary visual hallucinations, esp in contralateral hemifield; blindness; sensation of eye mvmt, eye deviation (contralateral or ipsi); forced blinking; variable spread to PL (sensory sx), TL/OL (formed visual hallucinations), mesial TL	Somatosensory auras; receptive aphasia (dom hem); neglect (nondominant hem); variable spread to OL (visual hallucinations), mesial TL, precentral regions (motor)

First Seizure of Life Evaluation

You will most commonly pick up a first seizure of life patient when they show up in your resident clinic after an ED visit. Your initial evaluation will focus on assessing for risk factors that suggest an elevated risk of future seizures (eg. Epilepsy), factors that will impact future therapy when you do begin to start a medication, and factors that suggest an elevated risk for non-epileptic events.

EPILEPSY

Please see "First Seizure of Life" Dorsata Pathway and refer ED providers to the First Seizure of Life Order Set.

Clinical History:

- Precipitants, prodrome, aura, duration
- Seizure semiology: loss or alteration of consciousness, fall, breathing, movements of head/face/limbs (stiffening, jerking, dystonic posturing), automatisms (oral, limb), eye movements, drooling or frothing, tongue biting, bladder/bowel incontinence
- Postictal: amnesia, confusion, aphasia, Todd's weakness, lethargy, headache, sleepiness

Risk factor assessment – features that can suggest elevated risk for recurrence or specific etiology:

- Mother's pregnancy history/birth history – looking for evidence of CNS insult (HIE, perinatal stroke/infection…)
- Febrile seizures (prolonged or multiple)
- Intellectual disability/developmental delay
- Prior CNS infection
- Stroke
- Vascular malformations
- Alcohol use and drug use
- Family history of seizures

Neurological exam:

- Often times pretty useless unless you can find something that suggests a focal lesion (videos of semiology are more useful for localizing seizure onset)

Counseling:

1) Driving

- REPORTING IS MANDATORY IN PA/NJ/DE
- The patient should not drive for 6 months following a seizure with loss of awareness. The reporting forms for PA/NJ can be found on the NeuroPenn website. They should be filled out and faxed in to the correct DMV (don't need to fill out all the identifying information at the top like SSI). Also on the DMV website, the password to DMV forms is "SafeDriver."
- The patient will receive paperwork in the mail about further steps. Based on information provided PennDOT will make a decision about placing restrictions on a person's driving.
- Special consideration which are officially determined by PennDOT's medical reviewers: seizure during med titration, nocturnal seizures, seizures preceded by aura.
- Patient's may drive with epilepsy ONLY if only nocturnal events or just after waking from 2 years, prolonged aura before all seizure for 2 years, recent breakthrough seizure was clearly provoked, recent breakthrough seizure was due to prescribed change in medication (but medication change must be reversed)

  You can always report for breakthrough seizure, PennDOT will review above criteria when deciding if patient can/can't drive
- Patients should contact PennDOT for further info about steps to get license back, which will usually require them to send you a form for you to fill out attesting to their seizure freedom
- One good resource is the Epilepsy Foundation State Driving Laws Database – www.epilepsy.com/driving-laws

2) Seizure safety

- Counsel patients to avoid situations where seizure would cause severe harm, such as open flames, swimming or bathing unattended, caring for small children unsupervised, operating heavy machinery, etc
    - Pro Tip: Most residents/Epilepsy attendings/Epilepsy fellows will have a dot phrase laying all this information out. Feel free to borrow these (consider this permission granted from Mike Baer) so you can give to patients in clinic, ward/EMU, and consult services.

3) Medications to avoid

DRUGS THAT LOWER SEIZURE THRESHOLD		
ANTIBIOTICS Penicillin (high dose) Cephalosporins (high dose) Quinolones (ciprofloxin, levofloxacin)* Metronidazole (Flagyl)* Imipenem, meropenem ***	**CHEMOTHERAPIES** Cyclosporine Erythropoetin Tacrolimus Zofran (ondansetron)	**PAIN MEDICINES** Tramadol Meperidine (Demerol)* Propxyphene (Darvon) Fentanyl
PSYCHIATRIC Lithium Bupropion (Wellbutrin)* Neuroleptics (esp. older Rx) Clozapine TCAs	**STIMULANTS** Amphetamine Cocaine* PCP Pseudoephedrine* Phenylephrine*	**OTHER** Flumazenil* Theophylline Diphenhydramine (Benadryl)
NEUROLOGICAL Mitoxantrone Ampyra Baclofen		*major offenders

4) Support Groups/Family Resources

- The Epilepsy Foundation (www.Epilepsy.com); Epilepsy Foundation of Eastern PA, 215-629-5003. Surrounding areas/states all have programs too.

Workup:

The goal here is to identify features suggestive of elevated seizure recurrence risk and to stratify patients into epilepsy subtypes – focal versus generalized

1)MRI head with epilepsy protocol: provides coronal images to evaluate for mesial temporal sclerosis

NOTE: contrast is not routinely indicated, unless you have a suspicion for a neoplastic/infectious/autoimmune etiology

2)Routine EEG: Can order as <1 hr routine EEG. Ideally captures sleep to improve chances of capturing epileptiform discharges. Note that outpatient EEGs are longer and use more provoking maneuvers (HV/Photic) than inpatient EEGs so they are typically preferred. Performed in the Perelman Clinic. To arrange as outpatient place order in Epic; the secretary will call the patient to schedule an appointment, but patient can also call 215 662 2661.
3)Ambulatory EEG: 24-48 hour EEG often used to capture events. Usually need to get a routine EEG first. Often will need ambulatory EEG before doing an EMU stay.

When to start an ASM

Basic principle – every patient who has epilepsy should be started on an antiseizure medicine because they will keep seizing without treatment. Therefore, every patient who has a second unprovoked seizure should be treated (risk of further seizures is above 70% over 4 years in some studies).
While we do not routinely start ASMs on patients after a single unprovoked seizure (risk of recurrence is about 30% over 5 years, assuming normal workup; and starting ASMs early does not change long term outcomes) several data pieces from your initial history and workup can suggest an ***elevated risk mandating early treatment before the second lifetime seizure:***

- **MRI abnormality or remote symptomatic cause:** brain tumor, brain malformation, gliotic tissue from old cortical stroke or injury from TBI, TBI with loss of consciousness, prior brain surgery with cortical injury, prior bout of meningitis/encephalitis
- **First seizure occurring during sleep:** Associated with 2-2.5 fold increased risk for seizure recurrence
- **Epileptiform abnormalities on EEG**: *Interictal epileptiform discharges, lateralized periodic discharges, generalized periodic discharges* are never normal except in rare circumstances. If you send off a routine EEG and get these back in the report, you will likely be starting an ASM for your first-time seizure patient. If the report is hedgy about calling something epileptiform then you can always discuss it with the reading epileptologist. Summary later in this section.

- NOTE: generalized and focal slowing are non-specific findings and generally do not warrant starting an ASM. For example, continuous, focal slowing indicated a structural lesion in 2/3 of patients, but seizures only occurred in 20% of patients.

Benign EEG variants

	Patient: age / state	Waveform: morphology / frequency	Duration	Distribution
Benign spike-like patterns				
Small sharp spikes	Adults / drowsiness and light sleep	Monophasic or diphasic spikes	Phase <50 msecs	Bi-hemispheric maximal-anterior / mid temporal
Wicket spikes	Adults / drowsiness and light sleep	Sharply contoured arch shaped / 6 to 11 Hz	Few seconds	Bilateral anterior / mid temporal
14- and 6-Hz positive bursts	Children and adolescents / drowsiness and light sleep	Arch shaped positive sharp component / 4-7 Hz and 13-17 Hz range	Less than 1 to 2 seconds	Bilateral posterior temporal / parietal
6 Hz spike and wave	Adolescents and young adults / relaxed wakefulness and drowsiness	Low voltage spike-high amplitude slow wave / 5 to 7 Hz	1 to 2 seconds	Generalized / at times maximal anterior or posterior
Rhythmic patterns with an epileptiform morphology				
Rhythmic temporal theta bursts of drowsiness	Adolescents and young adults / relaxed wakefulness and drowsiness	Notched flat topped / 5 to 7 Hz	Seconds	Bilateral temporal
Subclinical rhythmic EEG discharge in adults	Adults >50 / hyperventilation, drowsiness	Rhythmic sharply contoured / 5 to 6 Hz	40 to 80 seconds	Bilateral parietal / posterior temporal
Midline theta rhythm	Children and adults / awake, drowsy	Sinusoidal, arciform / 5 to 7 Hz	4 to 20 seconds	Midline, maximal centrally

Reproduced with permission from: Mushtaq, R, Van Cott, AC, Benign EEG variants. Am J Electroneurodiagnostic Technol 2005; 45:88. Copyright ©2005 American Society of Electroneurodiagnostic Technologists.

UpToDate®

From Moeller et al. "Electroencephalography (EEG) in the diagnosis of seizures and epilepsy." UpToDate.

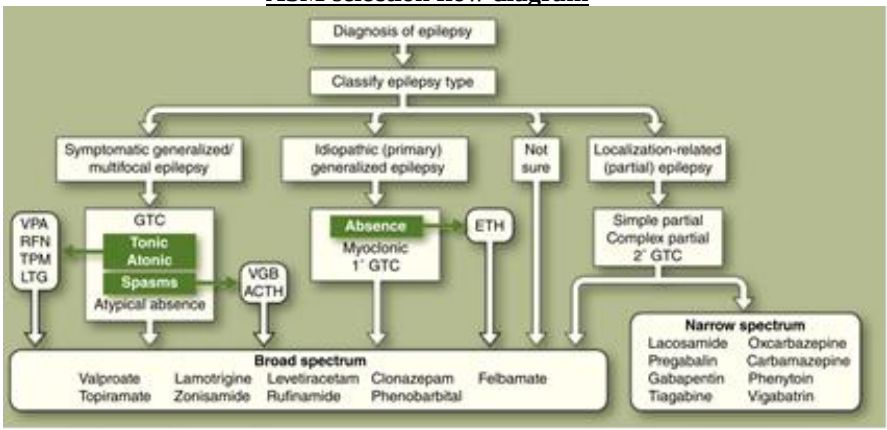
Which ASM should I start?

General Principles to consider:

- Seizure type: focal onset (use narrow spectrum ASMs) versus generalized seizures including myoclonic and absence (use broad spectrum ASMs)
- First ASM: choose wisely, as patient's may be on this for many years. Just under 50% become seizure free with first ASM
- Other meds: consider interaction with non-ASM meds
- Female: Childbearing years? Taking OCPs? Bone health? Teratogenic effects of ASM? See Pregnancy section below
- Elderly: use lower doses and titrate slowly, may experience side effects at lower doses. Protein bound drug doses may need to be lowered as albumin decreases with age. CrCl and hepatic clearance decrease after 65.

EPILEPSY

ASM selection flow diagram



ASMs for Idiopathic Generalized Epilepsy			
Monotherapy			
Setting	**GTC**	**Absence**	**Myoclonic**
Mono #1	VPA > LTG, TPM	VPA, ESX > LTG	VPA
Mono #2 after VPA	LTG > TPM, LEV > ZNS	ESX, LTG	ZNS, LEV, TPM
Mono #2 after LTG	VPA > TPM, LEV > ZNS	VPA, ESX	VPA > ZNS
Mono #2 after TPM	VPA, LTG	VPA, ESX > LTG	VPA
Combination Therapy			
Current ASM		**Consider Adding**	
FBM		VPA > LTG	
LTG		VPA, TPM, LEV, ZNS	
LEV		VPA > LTG, TPM	
TPM		LTG, VPA > LEV	
VPA		LTG > TPM, LEV, ZNS	
ZNS		LTG, VPA > LEV	

Vagus nerve stim	VPA > LTG, TPM

ASMs for Localization-Related Epilepsy	
Initial Monotherapy	
Focal aware	CBZ, OXC > LTG, LEV
Focal impaired awareness	CBZ, OXC > LEV
Secondary generalized	CBZ, OXC > LTG, LEV
Second Monotherapy	
First ASM	**Consider Next**
CBZ	LTG > LEV, TPM
LEV	LTG, CBZ, OXC > TPM
OXC	LTG > LEV, TPM
PHT	LTG > LEV, CBZ
TPM	LTG, CBZ, OXC > LEV
VPA	LTG, CBZ, OXC, LEV, TPM
Combination therapy	
Current ASM	**Consider Adding**
CBZ	LEV > LEG, TPM, ZNS
LTG	LEV > TPM, OXC, CBZ, ZNS
LEV	LTG, CBZ > OXC, TPM, ZNS, VPA
OXC	LEV > LTG, TPM, VPA, ZNS
PB	LTG, LEV > OXC, CBZ, TPM
PHT	LTG, LEV > TPM, BPA
TGB	LTG > LEV, TPM, OXC, CBZ
TPM	LTG, LEV > CBZ, OXC, VPA
VPA	LEV > OXC, LTG, CBZ, TPM
ZNS	LTG, LEV, OXC, CBZ

Influence of comorbid conditions on ASM choice	
ASMs to use cautiously or avoid	
Absence szs	CBZ, OXC, TGB
Anorexia/malnourished	FBM, TPM, ZNS
Arrythmias	CBZ, PHT, CLB

Bleeding diathesis	VPA
Blood dyscrasias	CBZ
Generalized szs	GP, CBZ, OXC (may exacerbate)
Hepatic disease	VPA, PHT, PB, CBZ, LTG, ZNS, FBM
Hypersensitivity reactions	ASMs with risk of rash (esp PHT, CBZ, LTG)
Hyponatremia	CBZ, OXC
Hypothyroid	CBZ, OXC, PHT
Myoclonic seizures	GPB, LTG, OXC, CBZ, TGB, PGB
Nephrolithiasis	ZNS, TPM
Obesity	VPA, PGB, ?CBZ, ?GBP
Oral contraceptive use	CBZ, OXC, PHT, PB, TPM (at dose >200 mg)
Osteopenia	PHT > CBZ, PB
Pancreatic disease	VPA, CBZ
Peripheral edema	PGB
PCOS	VPA
Psychiatric disorders	LEV, PB
Renal impairment	LEV, GBP, PB, PGB, TPM, ZNS
ASMs that may help the condition	
Headache	TPM, VPA, CBZ in children
Insomnia	TGB
Mood instability	OXC, VPA, LTG, CBZ
Neuropathic pain	GBP, OXC, CBZ, TPM
Obesity	TPM, ZNS
Periodic limb movements of sleep	CZP, GBP, TPM, ZNS
Tremor	CZP, PBT, PRI, ELV, TPM

ASMs for special circumstances	
Depressed patients	
IGE	LTG > VPA
Focal	LTG > OXC
Elderly	
Focal	LTG > LEV
Hepatic disease	
IGE	LEV, LTG
Focal	LEV
HIV +	
IGE	LTG, LEV
Focal	LTG, LEV
Renal disease	

IGE	LTG, VPA
Focal	LTG
Women who might become pregnant	
IGE	LTG > LEV
Focal	LTG > LEV, OXC

All four tables above adapted from Westover et al. "Pocket Neurology: Second Edition." 2016. For drug abbreviations please see "anti-epileptic drugs" table below.

Several take-aways:

- You will almost always be starting Keppra as an initial first line, often because you are gathering epilepsy patients from your time in the hospital, and Keppra is broad spectrum, low interactions/side effects, and can be loaded.
- Trileptal is a fine first line choice for focal epilepsy (suggested by clinical history, imaging, or EEG) and can be uptitrated relatively quickly (but still takes at least several days to a week to reach a good level).
- Lacosamide is easy to load and often well tolerated, but typically not our first line and it can be very expensive (go to manufacturer website for coupons) and they can help bring down the cost.
- As indicated in handy charts above, Lamotrigine is a great option. It is well-tolerated and safe in pregnancy. Obvious barrier is need to titrate up slowly to reduce risk of serious drug rash.

Anti-Seizure Medications					
ASM	**Mechanism**	**Initial dose/escalation**	**Therapeutic level**	**Total daily dose range, adults**	**Dose schedule**
Brivaracetam /BRV (Briviact)	Binds to SV2A	50mg BID ↑ 25-50mg BID q7-14 days if necessary		Up to 150mg BID	BID

Cannabidiol/CBD (Epidiolex)	Unknown	2.5 mg/kg twice daily ↑ 2.5mg/kg BID q7-14 days if necessary		total 20 mg/kg per day (25mg/kg total for TSc patients)	BID, consistently in fasted or fed state
Carbamazepine/CBZ (Tegretol, Tegretol XR)	(-)Na	100mg BID, ↑ 100mg BID q3-5d	8-12	600-2400mg	BID-QID (BID XR)
Cenobamate/CEN (XCopri)	(-)Na, (+)GABA	12.5 mg qHS ↑ follow dosepak, 100mg qHS in 8 weeks		100mg qHS-400mg qHS	qHS
Clobazam/CLB (Onfi)	(+)GABA	50-10mg qD, ↑5mg qd q7d	-	10-60 mg	BID
Eslicarbazepine/ESL (Aptiom)	(-)Na	400mg qd, ↑400mg qd q7d	-	400-1200mg	QD
Esogabine/EZG (Potiga)	(+)KCNQ (+)GABA	100mg TID, ↑100mg TID q7d	-	300-1200mg	TID
Felbamate/FBM (Felbatol)	unknown	300 mg TID, ↑300mg TID q7d	60-80	2400-4800mg	BID-TID
Gabapentin/GBP (Neurontin)	(-)Ca	300mg QD ↑to 300mg TID, then 300 mg TID q7d	12-25	900-6000mg	TID-QID
Lacosamide/LCM (Vimpat)	(-)Na	50mg BID, ↑100mg qd q7d	5-10	200-400mg	BID
Lamotrigine/LTG (Lamictal)	(-)Na	25mg QD, ↑depending on other ASMs, see LexiComp	10-20	100-500mg	BID
Levetiracetem/LEV (Keppra)	Binds to SV2A	250mg BID, ↑25-500mg BID q7d	20-40	1000-4000mg	BID
Oxcarbazepine/OXC (Trileptal)	(-)Na	150mg BID, ↑-300mg BID q7d	12-35	900-2400mg	BID-TID
Perampanel/PER (Fycompa)	(-)AMPA	2mg qhs, ↑2mg qhs q7d	-	1-12 mg	QHS
Phenobarbital/PB (Luminal)	(+)GABA	30-60mg QD, ↑30-60mg q1-2wk	20-40	60-240mg	QD-BID
Phenytoin/PHT (Dilantin)	(-)Na	200-300mg QD, (oral load 6-7 mg/kg q8h x 3 doses)	10-20 total, 1.0-2.0 free	200-500mg	QD-BID
Pregabalin/PGB (Lyrica)	(-)Ca	75mg BID ↑75mg q1-2wk		600mg daily total	BID -TID
Tiagabine/TGB (Gabitril)	(+)GABA	4 mg QD, ↑4-8mg BID-TID qwk	-	32-56mg	BID
Topiramate/TPM (Topamax)	(-)Na (+)GABA (-)NMDA	25-50mg QD, ↑5mg BID q1-2wk	8-25	100-600mg	BID
Valproate/VPA (Depakote)	(-)Na (-)Ca (+)GABA	125-250mg BID, ↑125-250mg BID qwk	80-100	1000-4000mg	BID-TID

Rufinamide/RUF (Banzel)	(-)Na	200-400mg BID, ↑400 to 800mg qday q2d	-	1600-3200mg	BID
Vigabatrin/VGB (Sabril)	Inhibits GABA transamin ase	500 mg BID, ↑500mg qd q7d	-	1-3g	BID
Zonisamide/ZNS (Zonegran)	(-)Na (-)Ca	100-200mg QD, ↑100mg QD q7d	20-30	200-600mg	QD-BID

ASM monitoring considerations

Extended release formulations are absorbed in the GI tract more slowly (half-life remains the same), so there are fewer fluctuations in peaks/troughs
Enzyme Inducers: Phenobarbital, Phenytoin, Carbazmazepine, Oxcarbazepine (weak), Topiramate (weak)
Enzyme Inhibitors: Valproic acid

Protein Bound: Phenytoin, Valproic acid
(free levels may be higher than expected in hypoalbuminemia; lower than expected in uremia)

Monitoring: Check ASM levels, CBC, liver, renal function at least yearly while on chronic therapy
Calcium/Vitamin D: Due to risk of osteoporosis with all chronic ASM therapy, all patients should take Ca2+/Vit D supplementation when taking PHT, PHB, CBZ, VPA, TPM, OXC, as well interval DEXA scans (every 5 years if normal, every 2 years if abnormal, referral to endo/rheum if osteoporosis)
Folic Acid: Should be prescribed to all women of childbearing age on ASMs (0.4-0.8mg/day folic acid). If taking CBZ or VPA, take 4mg/day for 1-3 month prior to conception. Counsel regarding contraception and family planning. If a patient becomes pregnant do NOT stop medications.

Common anti-epileptic drugs and approximate inpatient lab result times

In house tests	Send out tests
· Brivaracetam [Briviact] *order as Levetiracetam level* → Mon/Wed/Fri by 5PM · Carbamazepine [Tegretol] → 60 minutes · Lamotrigine [Lamictal] → Mon/Wed/Fri by 5PM · Levetiracetam [Keppra] → Mon/Wed/Fri by 5PM · Phenobarbital → 1-6 hours · Phenytoin [Dilantin] → 1-6 hours · Primidone [Mysoline] → 24 hours · Topiramate [Topamax] → Mon/Wed/Fri by 5PM · Valproate/Divalproex [Depakene/Depakote] →1-6 hours · Zonisamide [Zonegran] → Mon/Wed/Fri by 5PM	· Clobazam [Onfi] → 1-4 days · Eslicarbazepine [Aptiom] → 1-4 days · Ethosuximide [Zarontin] → 1-5 days · Felbamate [Felbatol] → 1-4 days · Gabapentin [Neurontin] → 1-4 days · Lacosamide (Vimpat) → 1-4 days · Oxcarbazepine [Trileptal] → 1-4 days

ASM side effects

EPILEPSY

ASMs	COMMON EFFECTS	RARE SIDE EFFECTS	METABOLISM
Carbamazepine (Tegretol, XR, Carbatrol)	**Ataxia**, dizziness, diplopia, **hyponatremia**	**Aplastic anemia**, agranulocytosis, rash, SJS, hepatitis	95% hepatic
Clobazam (Onfi)	Drowsiness, aggression, URI, ataxia, sialorrhea	Aggression	95% hepatic, metabolite renally excreted
Eslicarbazepine (Aptiom)	Dizziness, drowsiness, ataxia	Hepatotoxicity, SJS	90% renal
Ezogabine (Potiga)	Dizziness, drowsiness, fatigue	Neutropenia, thrombocytopenia, nephrolithiasis	85% renal
Felbamate (Felbatol) limited	Insomnia, headache, wt loss, N/V	Aplastic anemia, hepatotoxicity, rash, SJS	50/50
Gabapentin (Neurontin)	Weight gain	Movement disorders, behavior abnl (children)	100% renal
Lacosamide (Vimpat)	Dizzy, headache, fatigue, N/V, ataxia/tremor	rare	50/50
Lamotrigine (Lamictal)	Headache, dizziness, insomnia	Rash, **SJS**	80% hepatic
Levetiracetam (Keppra)	Irritability	Psychosis	70% renal
Oxcarbazepine (Trileptal)	Dizziness, GI disturbance, **hyponatremia**	Rash, SJS	50/50
Perampanel (Fycompa)	Dizziness, HA, ataxia, mood changes/anger	blurred vision/diplopia, hyponatremia	95% hepatic, 20% renally excreted
Phenobarbital (Luminal)	Sedation, irritability, depression	Rash, SJS, hepatitis, connective tissue disease	75% hepatic
Phenytoin (Dilantin)	Ataxia, hirsutism, coarse facies, gingival hyperplasia	Rash, SJS, hepatitis, lupus-like reaction	95% hepatic
Pregabalin (Lyrica)	**Weight gain**, edema, rash, incr CPK	Severe edema, rash, SJS	>90% renal
Rufinamide (Banzel)	Shortened QT (50%), HA	**Shortened QT**	95% hepatic
Tiagabine (Gabitril)	Irritability, anxiety, weakness	Spike-wave stupor	95% hepatic
Topiramate (Topamax)	↓ verbal fluency, ↓ memory, **wt loss**, paresthesias, hypohidrosis	Acute angle closure glaucoma, renal calculi	80% renal
Valproate (Depakote, ER, Depakene)	Tremor, **wt gain**, hair loss, GI Sx, diarrhea (Avoid in pregnancy!)	Hepatotoxicity, pancreatitis, thrombocytopenia	95% hepatic
Vigabatrin (Sabril)	Somnolence, headache, **visual field constriction**, otitis media, dizziness	Visual field constriction --> d/c drug immediately!	Urine (80% unchanged)

Common issues of all old school drugs (phenobarb, valproic acid, phenytoin, carbamazepine):

- **Rash**, fatigue, **suicidal ideations** (screen all patients!)
- Require monitoring of drug levels (narrow therapeutic window)
- P450 metabolism, lots of drug interactions
- Acute toxicity: sedation, nausea/vomiting, ataxia
- Chronic side effects: hepatotoxicity, marrow suppression, decreased vitamin D (osteoporosis)

What do I do if my patient wants to become pregnant?

BEFORE PREGNANCY:

- -Verify need for ASM
- -Determine "best" ASM for individual patient

- -Seizure control must be maintained (6 mos. freedom on current regimen is optimal)
- Monotherapy preferred at lowest effective dose
- -No depakote if at all possible
- Folate supplementation (0.4 - 4 mg)

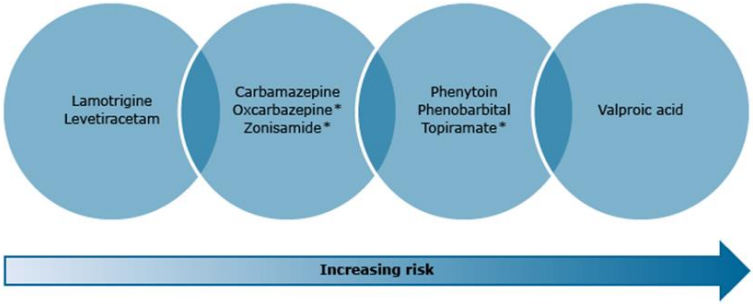
DURING PREGNANCY:

- Ask patient to enroll in nationwide registry (http://www.aedpregnancyregistry.org/)
- Monitor ASM levels (free levels) monthly starting at 8 weeks, expect dose adjustments
  -Free drug levels are more reliable during pregnancy for highly protein bound ASMs – phenytoin, phenobarb, valproate, carbamazepine
- Can expect lamotrigine/keppra/oxcarbazepine levels to decrease due to increased clearance
- Screening for malformations (fetal ultrasound level 2, AFP)
- Vitamin K during last month (controversial)
- For new seizures during pregnancy/failed outpatient regimen start Keppra
  - From current registries risk of malformations .4-2.7% while on keppra (background 3-4% risk of malformations in general population)

AFTER PREGNANCY:

- Starting day 3 after delivery can begin to taper ASM doses
  -Decrease lamotrigine/keppra (can do the same for other meds cleared by hepatic glucuronidation – gabapentin, lacosamide, oxcarbazepine, pregabalin, topiramate, valproic acid) over two to three weeks postpartum
  -Medications metabolized by cytochrome P450 enzymes (eg. Carbamazepine, clobazam, ethosuximide, felbamate, perampanel, phenobarb, phenytoin, primidone, tiagabine, zonisamide) can be tapered more slowly over 6 weeks
- Counsel mother on holding baby, bathing baby alone (no-no), etc.
- Breastfeeding is encouraged with all ASMs

Teratogenic risk profiles of antiepileptic drugs

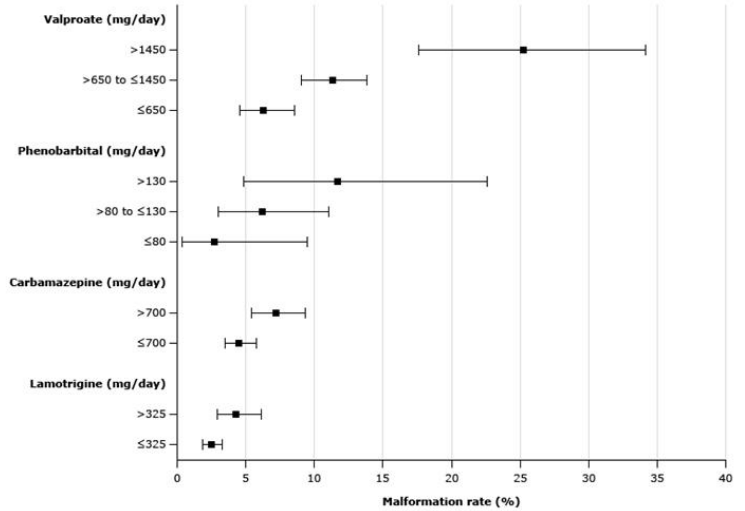


Summary of relative teratogenic risk profiles of antiepileptic drugs, based on available data. The risk profiles include data about major congenital malformations, fetal growth, and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of patients studied, and confidence intervals.

LTG: lamotrigine; LEV: levetiracetam; CBZ: carbamazepine; OXC: oxcarbazepine; ZNS: zonisamide; PHT: phenytoin; PB: phenobarbital; TPM: topiramate; VPA: valproate.
* Neurodevelopmental outcomes are not yet known.

EPILEPSY

Malformation rates for four antiepileptic drug monotherapies at different doses at conception



Rate of congenital malformations for the four monotherapies (valproate, phenobarbital, carbamazepine, and lamotrigine) at different doses at conception. Black squares indicate rate for each drug and dose; horizontal lines indicate corresponding 95% confidence intervals.

Data from: Tomson T, Battino D, Bonizzoni E, et al. Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry. Lancet Neurol 2018; 17:530.

Modified from: Tomson T, Battino D. Teratogenic effects of antiepileptic drugs. Lancet Neurol 2012; 11:803. doi: 10.1016/S1474-4422(12)70103-5. PMID: 22805351.

UpToDate®

OCP-ASM interaction		
ASM decreases OCP c/f contraceptive failure Rx: OCP w/ > 50 mcg ethinyl estradiol	OCP decreases ASM c/f breakthrough seizure	No Known Interaction
Phenobarbital Phenytoin Carbamazepine Eslicarbazepine Oxcarbazepine Topiramate (if >200mg qd) Felbamate Primidone Perampanel Rufinamide Onfi	Lamotrigine	Phenobarbital Phenytoin Carbamazepine Eslicarbazepine Oxcarbazepine Topiramate (if >200mg qd) Felbamate Primidone Perampanel Rufinamide Onfi

What should I do if my patient keeps having seizures?

1) Identify precipitants

- Most common provoking factors are medication non adherence (see below), infection, and substance use
- Assess if seizures appeared the same or if this is a new semiology
- If there is evidence of an infection you can do a benzo bridge to get them through the period of heightened seizure susceptibility

-Chlorazepate (Tranxene) 3.75 mg BID x 5-7 days
-Clonazepam (Klonipin) 0.5 mg BID or TID x 5-7 days

- Other provoking factors: Fever, stress/fatigue, sleep deprivation, stimulant drugs, alcohol withdrawal, hypoglycemia, electrolyte disturbances, hypoxia, stroke, head trauma, CNS infections

2) Improving adherence to ASM regimens

ASM non-adherence is a very common issue – across all diseases 50% of patients will miss doses of medications. Studies of epilepsy patients have shown that between 26 and 79% miss 3 or more doses of medication per week.
Risk factors for non-adherence include: increasing number of daily doses, polytherapy, late adolescence/early adulthood, anxiety, lower SES

Approaches

1) Smart phone apps – variety of free apps to choose from
2) Pill boxes – can often find free ones in the resident workroom/EEG reading room
3) Home health care – nursing visits can assess barriers to ASM adherence and improve patient/caregiver education
4) Extended release/once daily dosing may help
5) Longer refills – 3 months versus 1 month – can help if patients often lapse around times of refills/have problems with monthly paychecks

3) When and how to escalate therapy

Unfortunately, many patients will continue to have seizures despite compliance with ASMs.

- Seizure freedom with first drug monotherapy– 50%
- Seizure freedom with second drug monotherapy – 10%
- Seizure freedom with third drug monotherapy – 1%

Further trials of medication monotherapy

After failure of a first medication, a second medication monotherapy may be attempted (see chart above for choice of second line agents). Most of the time you will get the second medication up to therapeutic levels before slowly weaning off the first medication over the course of weeks.

- Most patients will have a temporary increase in side effects during titration up of the second drug, but this should improve with time. It is important that they know this so they don't stop the cross titration.

Combination therapy

If a patient continues to have seizures despite adequate monotherapy trials, you may need to jump to combination therapy. This often fails, however, and only 10-15% of patients will achieve seizure remission after failing monotherapy.

- See above charts for guidance about how to add additional medications. You will want to balance similar side effects and mechanisms, drug-drug interactions, cost, and other comorbidities when you select additional ASMs.

4) Medically refractory Epilepsy and surgical evaluation and options

EPILEPSY

Once a patient has failed more than 2 ASMs they are very unlikely to acheive seizure freedome with further ASM trials (less than 5%). Therefore, once a patient has failed 2 ASMs candidacy for epilepsy surgery should be considered. If you have a patient who is poorly controlled discuss the possibility of epilepsy surgery when staffing with an epilepsy attending in resident clinic – they may be able to help you coordinate the initial series of evaluations (see EMU section below).

Who are the best candidates for epilepsy surgery?

- Mesial temporal lobe epilepsy (often with accompanying mesial temporal sclerosis)
- Lesional epilepsy (like low grade glial tumors)
- Focal epilepsy that can be localized with intracranial EEG/metabolic brain imaging

NOTE: even generalized epilepsies have surgical option – see neuromodulation below

Types of epilepsy surgery

1) Resection – continues to be the gold standard, requires localization of seizure focus and safe distance from eloquent tissue (or at least the risk of significant functional impairment from resections needs to be outweighed by the benefit of better seizure control).
2) Thermal ablation – again can be used if a seizure focus is localized and is a safe distance from eloquent tissue. Ablation is used when the area is not easily accessible via open surgery. Variations include laser ablation and ultrasound induced ablation.
3) Neuromodulation -- epileptogenic focus is in eloquent cortex (VNS or RNS) or epilepsy is generalized (VNS)

- Vagal Nerve Stimulator (VNS): Vagal nerve stimulator are battery powered devices that stimulate the vagus nerve. Responsive models exist that provide stimulation in response to an increased heart rate often associated with seizures.

  Effectiveness: 50-60% of patients will have a >50% reduction in seizure frequency
  Contraindications: Arrhythmias, cardiac conduction abnormalities, sleep apnea (relative contraindication), programmable shunt valves (due to VNS magnet messing with the valve settings)
  Side effects: Voice alterations (can lower the pulse width of stimulation), vocal cord paralysis (from intra-op manipulation, most recover), bradycardia
- Responsive Neurostimulation (RNS): RNS is used if you have 1-2 seizure foci that cannot safely be resected. The RNS has a small battery pack that sits in the skull, which can support up to 2 depth electrodes which both record

Psychogenic non-epileptic events

30% of patients with seizure disorder also have PNEE, up to 40% in tertiary referral centers such as HUP
Scalp EEG has many limitations so it is not definitive for PNEE

- Minimum $6cm^2$ of epileptic cortex in order to be picked up by scalp EEG
- Routine EEG more sensitive for temporal lobe seizures and less sensitive for frontal lobe seizures (due to electrode placement -- if c/f frontal lobe seizure, t/b EEG fellow and request different channel set up)
- Intracranial electrode monitoring is typically reserved for pre-surgical patients, not patients in whom PNEE is thought possible

In general, several ictal phenomena are more concerning for PNEE than for epileptic seizures

- Fluctuating course, pauses
- Changes in stereotyped event (or absence of stereotyped event)
- Pelvic thrusting (not unusual for frontal lobe seizures!)
- Response to verbal stimulus
- Only occur during wakefulness or drowsiness

- Recollection of the event
- Eyelids shut with eyes rolled back in head (not to be mistaken for gaze deviation!)

Table 3
Ictal phenomena of PNES versus ES: Video/EEG features.

Clinical features	Psychogenic seizures	Epileptic seizures
Onset [8,10,17,19–21]	Gradual, during wakefulness or pseudo-sleep	Abrupt, during wakefulness or sleep
Duration [8,17–21,24,25]	Variable, often >2 min	Up to 1–2 min
Response to verbal stimulus [17,39]	Common	Never preserved in GTCS; rarely and only partially preserved in CPS
Upper and lower extremity out-of-phase movements [18,24,25,27]	Occasional/very common	Rare in GTCS
Thrashing, violent movements of the entire body [19,20,25,26]	Occasional/common	Occasional/common in FLS; rare/very rare in GTCS
Side-to-side head movements and side-to-side body turning [10,18,21,24,25,27]	Occasional/common	Occasional/ common in FLE; rare/very rare in GTCS
Unilateral head turning [21,25,27]	Rare/occasional	Common preceding GTCS
Pelvic thrusting [8,18,21,24–29]	Occasional/ common (forward)	Occasional/common in FLS; rare/very rare in GTCS (backward)
Whole-body rigidity [25]	Rare/occasional	Always present in the tonic phase of GTCS
Fluctuating course; pauses in motor activity [8,17]	Common	Very rare
Opisthotonic posturing [10,17,18,20]	Occasional	Absent
Vocalization [10,18,21,24,25,27,28]		
Timing	At the start or throughout the spell	Usually in the middle of GTCS
Features	Emotional content	Monotonous epileptic cry in GTCS/ continuous, moans, animal-like noises, uttering in FLS
	Ictal stuttering (rare)	
Eye closure [14,17–19,26,30,33,34]	Common/very common	Rare/very rare
	Forceful	Never complete nor forceful
Tongue biting [8,18,26,31,34,35]	Very rare, on the tip	Occasional/common, in GTCS, on the side
Incontinence [8,10,16,18,26]	Very rare	Common in GTCS
Prolonged unresponsiveness without prominent motor features [8,10,16–19,26,27]	Occasional	Very rare
Ictal heart rate [38,39]	Not significantly increased	Increased in CPS, GTCS
Postictal memory [27]	Common	Very rare
Postictal confusion [24]	Occasional	Common/very common
Postictal breathing pattern [24,37]	Rapid, shallow irregular, with pauses	Stertorous breathing after GTCS; quiet, shallow, regular after FLS

Note. Figures for the frequency of these features are approximate: very common, >70%; common, 30–70%; occasional, 10–29%; rare, 5–9%; very rare, <5%. GTCS, generalized tonic–clonic seizures; CPS, complex partial seizures; FLS, frontal lobe seizures.

From Mostacci B, et al. Ictal characteristics of psychogenic non-epileptic seizures: What we have learned from video/EEG recordings—A literature review. Epilepsy & Behavior. 2011;22:144-153.

The Epilepsy Monitoring Unit

HOW TO REFER FROM CLINIC:

1. Put in an order for EMU CONSULT (type EMU into the orders section in PennChart)
2. Indicate reason for referral in your clinic note: (one of the 3 reasons below)
3. All patients need recent outpatient EEG (for insurance approval) and sometimes a recent brain MRI
4. CC your EMR chart to Florence (Delight) Roberts with best number to reach patient
5. Delight will do prior auth and schedule the patient. Please call her (662-7294) or email her with all ?/concerns: delight.roberts@uphs.upenn.edu

TYPICAL ADMISSIONS:

1) Differential Diagnosis (Epileptic vs. non-epileptic events)

- Goal is to capture a spontaneous event so ASMs are weaned completely.
- If no spontaneous event occurs they are induced with photic stimulation and hyperventilation
- The majority of patients with non-epileptic events are subconsciously expressing psychological stress from some form of trauma, often sexual, physical, or emotional abuse, or other traumatic events.

- Once they are given the diagnosis and they understand the underlying problem, approximately 50% of patients are completely cured of their non-epileptic events, or they are substantially reduced
- Early psych intervention is of great benefit for non-epileptic events, so all patients are referred to a psychiatrist as an outpatient, or as an inpatient when appropriate. The new policy of the psych department is for us to provide the patient with their clinic number at 3535 Market St. (866-301-4724)
- It is uncommon for patients to malinger and "fake" their seizures for secondary gain.

2) Presurgical Evaluation

- For patients with refractory partial epilepsy (failure of adequate seizure control after trying 2-3 ASMs) that significantly impacts quality of life. Pre-surgical evaluation may consist of THREE phases:

PHASE 1: The patient is placed on continuous video-EEG monitoring.

- Day of arrival: They are NOT sleep-deprived. Check the preadmission orders for medication taper plan.
- Goal of capturing 3 (ideally spontaneous, though may require induction) is optimal for presurgical monitoring. The patient's data is then presented at Epilepsy Surgical Conference at a later date, the epilepsy fellow will order remaining testing needed on discharge.

PHASE 2: Intracranial evaluation.

- Neurosurgery places intracranial grid, strip, bilateral hippocampus depth electrodes, or a combination of the latter. Patients must be carefully monitored. All patients get SQ heparin, TEDS and compression boots.
- Once enough seizures are captured, patients are re-presented at Epilepsy Conference. They are either continued on monitoring, undergo cortical stimulation, or explanted. Electrode removal is done by neurosurgery (check with them the day before to ensure all necessary labs and type and screens are sent). After explantation, the patient will typically stay in the EMU overnight for monitoring, and will be discharged when stable.

PHASE 3: Patients can have a resection, laser ablation or other procedure (e.g. RNS, VNS, DBS) after any of these phases. These decisions are made in the Epilepsy Surgical Conference on Thursdays. Patients are on the neurosurgery service post-op.

3) Classification

- Determination of seizure type (e.g. the patient is thought to have localization-related epilepsy, but also has generalized epileptiform discharges on EEG, and is failing treatment).
- Diagnosis guides treatment, as some ASMs are best for generalized Sz, while others (eg Tegretol) are avoided.

IMPORTANT INFORMATION FOR EMU ROTATION

1) Seizure safety and documentation

- Certain steps must be taken to reduce the likelihood of patient injury. Falls are the most frequent cause of injury in the EMU. High risk patients (eg- severe MR or dementia) may need family members staying with them or a 1:1. Reinforce the following rules to each patient on admission:

  "Don't get up out of bed without nursing help, including going to the bathroom, or going to sit in a chair."

"If you use the bathroom, a nurse or family member must wait outside the partially open door to assist in case of a seizure. There are no cameras in the bathroom."

"If you want to sit in the chair, please tell the nurse so the camera can be properly positioned."

- All admissions should have: PRN Tylenol for headache, PRN Ativan 2mg IV for seizure (this will be in EMU admission order set)
- All women of childbearing age must have a bHCG
- Write an event note including a description of seizure, especially things that may be missed on video, plus your exam and plan.
- If there is a question of ongoing seizures, speak to senior on call if at night.

2) <u>EMU ictal-post ictal exams and safety during seizures</u>

This is taught to all EEG techs and EMU nurses beginning June 2017. Designed by Ammar Kheder, Chloe Hill, & Susanna O'Kula and based on consensus to standardize ictal testing for better neuroanatomic localization, patient safety, and staff satisfaction.

1. SAFETY!!

When a seizure is identified (either seen on the monitor, button is pushed by patient or family, noticed by nurse) ensuring the scene is safe is key. Hopefully a nurse or tech will have done this already but if you are in the room when a seizure begins, check:

- the pads alongside the bed are in place and the bed rails are up
- the oxygen is working and ready to use if needed
- the suction is working and ready to use if needed
- If the patient is already convulsing, turning her on her side.

2. Light on, uncover patient, and check camera. Again, this ideally will be done before you arrive, but these steps are crucial to capture a good ictal exam on camera.

3. Assign examiner. The nurse or tech who is on the scene first will usually perform the exam and designate herself as the examiner. If you happen to be first, it's similar to a code scenario where you designate someone

4. "What do you feel right now?"

- if the patient can still speak to answer you, it indicates seizure onset does not involve his eloquent cortex even if later he generalizes and becomes unable to speak.
- she may say "I feel tingling in my right arm" or "I have a churning sensation in my stomach" or "I feel afraid." Often patients will forget these sensations later, so during or immediately post-ictal is a key time to elicit any type of sensory phenomena.

5. Describe what you see out loud

- particularly for elements not likely to be captured on camera: piloerection, diaphoresis, gaze deviation, oral automatisms

6. "Please repeat and remember purple elephant"

7. Ask patient to name an object

8. "What is your name? Where are you? What day is it?"

9. "Lift your arms" Ask the patient to lift her arms WITHOUT mimicking the gesture. If she does not respond or does something else (eg lifts her legs or touches her nose), mimic the correct gesture.

POST-ICTAL: The post-ictal exam is nearly identical to the ictal exam with two modifications. (10 and 11)

10. "Can you remember the words I gave you?"

11. "What was your last seizure? What did you feel?"

Asking this can help you assess whether or not the patient remembered her most recent seizure. Asking again about what she felt soon after a seizure may trigger a description of her sensory, visual, or auditory aura that has not been elicited before.
Repeat naming, orientation, motor commands (steps 7-9). Doing so allows you to assess how close the patient is to her neurologic baseline & assess for a post-ictal aphasia or Todd's (unilateral weakness).

3) <u>Seizure flurries/clusters</u>

- Increased seizure frequency is aggressively managed to prevent status epilepticus
- All patients will have standing orders with parameters for notifying MD of seizure frequency
- Observe closely for an accurate seizure count
- Monitor vital signs, cardiac rhythm, **obtain fingerstick glucose** and appropriate labs
- Continue benzodiazepines/consider restarting home medications for increased seizure frequency
- **If you are unsure if a patient is having too many seizures, call the fellow or attending (some attendings will let you know they want to be directly called in the case of a cluster**

<u>Common outpatient calls</u>

Problem: Dramatically increased seizure frequency over baseline

- Ensure return to baseline in between, no c/f status
- Assess for precipitants – infectious symptoms, sleep deprivation, stress, alcohol use
- ***Solution***: Prescribe rescue mediation (Ativan 2-3 mg daily), give extra dose of typical ASM (unless patient essentially maxed out already), if overnight and you think that a rescue benzo is appropriate but patient needs a prescription you can call to ask for a DEA if needed (can keep patient from unnecessary ED visit, and having an attending waking up for 5 minutes overnight is better than $5,000 in additional healthcare spending)

Problem: Patient has a rash

- Assess for concerning features – fever, facial involvement, mucosal involvement, edema, skin detachment, rapidly evolving, abdominal pain
- If the above – SEND TO ED to rule out SJS/DRESS and stop med with plan to switch to something else
- If none of the above can re-eval in 24-48 hours or order urgent outpatient derm evaluation

Problem: Called by lab to say that ASM levels are high

- In general if they are not having side effects and they have good seizure control then don't change the medication dose simply in response to high level – always call patient and make sure they are feeling okay.
- **Elevated PHT level** (therapeutic range 10-20)
  -Toxicity = fatal due to arrhythmia.
  -Intoxication causes ataxia, horizontal nystagmus, slurred speech, lethargy, confusion, coma (in order of worsening intoxication). Worsening toxicity noted as levels approach 30, severe intoxication seen above 30
  -Check phenytoin level and CMP with albumin (as PHT is a protein bound drug, would need free phenytoin level if patient has hypoalbuminemia)
  -If altered send to ED for EKG/serial phenytoin levels if c/f rapid rise in level due to zero order mechanics

-Chronic toxicity can be managed as an outpatient with changes in dose so long as patient can ambulate safely/has someone at home to assist with ADLs until toxicity resolve

Status Epilepticus

Status Epilepticus broadly refers to continuous seizure activity and is an emergency (in most cases). There are different types of status, broken down as:

Convulsive status epilepticus – EMERGENCY, treat immediately

- More than 5 minutes of continuous generalized seizure
- 2 or more discrete generalized seizures without incomplete recovery in between

NOTE: subset of convulsive status includes focal motor status, which in very refractory cases can include **epilepsia partialis continua (EPC), a condition of treatment resistant focal motor seizures without change in consciousness. Often caused by focal lesions and very difficult to treat solely with ASMs (much less of an emergency than generalized convulsive status, do not intubate a patient for EPC unless discussing with multiple other people first).

Non-convulsive status epilepticus – Less emergent, consider your options

- Generally occurring in patients who are already comatose (i.e. ICU consults) with no clear outward clinical signs, referring to continued electrographic seizures thought to be causing impairment of consciousness/awareness (i.e. treating the seizures improves mental status).

1) <u>Approaching a patient suspected to be in Status when called for a consult</u>

- **Is the patient still seizing?**
  -Ensure the team has started down the status pathway (access on Dorsata/Penn Pathways). Critical to get benzos on board as soon as possible followed by loading of an ASM – always remember to have the team order STANDING doses as well.
- **Assess airway**
  -Is the patient able to protect airway? Many times when you are called for a status consult the primary team will have already called a rapid response and anesthesia may be preparing to intubate the patient. Not every status patient needs to be intubated, and if on exam they appear to be post ictal (i.e. deeply sleeping) if they can be closely monitored with consistent recovery an intubation can be avoided. If there is doubt however, intubation is always safer

- **Is there a clear cause?**
  -All patients get CMP, CBC, UA, UDS (when in the ED), Chest X-ray, Viral studies (i.e. COVID)
  -All patients should be screened for alcohol abuse. Search PDMP for benzo prescriptions.
  -Common causes in patients with **preexisting history of epilepsy** = ASM non compliance and systemic infections. As long as seizure semiology is consistent with prior they may not need more workup
  -If patients **do not have a diagnosis of epilepsy** they need head imaging.
  Try to quickly get a stat head CT in ED or shortly after rapid response
  Less emergently can get MRI (contrast depending on clinical scenario)
  Don't forget about venous sinus thrombosis in right clinical context (i.e. status in pregnant patient) – evaluate with MRI brain w/wo contrast or CT venogram
  -**When to do LP?** Febrile, nuchal rigidity, status out of the blue, elevated WBC without clear cause, EEG with temporal lobes discharges w/o history of epilepsy,

prodromal psychosis. Doing an LP while treating with empiric abx/antivirals, new and severe psychiatric symptoms

- **Does the patient need LTM?**
  -Generally speaking, almost all patients who are suspected to be in status epilepticus will be placed on LTM (unless they are showing clear recovery in the minutes to hours after treatment and regain an exam). Below are several rationales for using LTM:

Indications for Continuous EEG

Indication/Setting	Rationale
Recent Clinical Seizure without return to baseline ▪ Not purposeful on exam (i.e. not withdrawing or localizing to pain) ▪ Subtle motor findings (look for nystagmus, mild facial/extremity twitching)	Convulsive seizures/SE can transition to non-convulsive seizures/NCSE after treatment in 20-50%.
Screening for Non-Convulsive Seizures (NCSz) or NCSE in at-risk patients ▪ History of epilepsy, acute brain injury (SAH, TBI, ICH), brain tumor, recent convulsive status epilepticus (CSE), fluctuating mental status, and paroxysmal events that are concerning for seizures, comatose patient, anoxic, intensive care unit (ICU) patient	NCSz/NCSE are prevalent in the critically ill and need EEG to detect.
Monitoring and treatment of known non-convulsive seizures	Characterization and quantification of events to adjust treatment
Abnormal routine EEG ● Epileptiform discharges or Periodic discharges	Higher risk of seizures
Loss of reliable exam in setting of clinical concerns for status (i.e. comatose, anoxic) ● Patient on continuous anesthetic infusion (i.e for refractory SE) ● Paralytic	Electro-clinical Dissociation, EEG will be the primary mean to detect seizures.

Reproduced from 2020-2021 Penn Neurocritical Care Guide

-However, LTM connections are generally not emergencies. In only 2 circumstances will the tech need to hook the patient up overnight:

1) Patient transferred from OSH with concern for status, arrives to NICU comatose
2) Clinical seizures stop but patient is left without an exam and we can't rule out non convulsive status

- At HUP techs will come in around 6 AM. If it's near the end of your night shift generally the hook up could wait until the first tech comes in.

CONTINUOUS EEG (LTM) GUIDELINES

LTM EEG requests only placed by the NICU fellow/attending or Neurology SAR/attending. Non-neurology or NICU services must contact Neurology consult team to request LTM (except for hypothermia hook-ups, which can only be requested from 7 am – 11 pm during the week and 7 am – 7 pm on weekends).
LTM reads via email at noon and 5 PM: EEG fellow will contact team with urgent reads, limit calls to EEG fellow
Process to obtain LTM:

- Place order in EPIC (type in LTM or EEG, select continuous)

- Send an email to EEGReaders@uphs.upenn.edu, with initials and MRN of the patient, and brief clinical history

AFTER HOURS LTM READING:

- New hook up screened by tech (20 min) and fellow will contact team ONLY if there is a concerning finding.
- TECH WILL EMAIL THE EEGREADERS email after every LTM hook-up.
- ALL TECHNICAL ISSUES: should contact tech directly (not fellow)
- Only patients in active STATUS EPILEPTICUS read after 5 pm (once at 9 pm, once 3 am if deemed necessary by the EEG fellow)
- BURST SUPPRESSION: must be monitored by in-house team
- Calls to the fellow:
    - Only from Neurology, NICU fellow or an attending (JAR must d/w SAR prior to call)
    - If it is at PAH after hours, call the Epilepsy fellow and then Specialty Care at 800-521-9757 who will hook the patient up
    - No non-urgent calls (see criteria below regarding when to hook up a patient to LTM) LTM guidelines:
- Criteria for requesting LTM after 5 PM
    - Transfer from an OSH for LTM and patient is comatose
    - Convulsions cease but patient has no exam (concerning for nonconvulsive status epilepticus)
    - multiple clinical events highly concerning for seizure (patient obtunded/comatose)
- LTM requests INAPPROPRIATE after 5 PM:
    - hypothermia (goal: hook up patient within 12 hours) -- ***ICU teams can request LTM connections when paralyzing patient's undergoing therapeutic hypothermia without Neuro consult unless there is clinic concern for seizures***
    - subarachnoid hemorrhage
    - patients not in coma (e.g. neurological exam able to rule out status epilepticus)

2) <u>Status Epilepticus pathway</u>

Not included this year due to size of pathway – recommend downloading Dorsata App or looking on Penn Pathways on intranet

In essence, a patient in convulsive status has ABC's stabilized, electrolytes checked, and IV Ativan 4 mg or IM versed 10 mg administered x 1, with second round given with continued seizures after 5 minutes. Next patient will be loaded with IV Keppra 3 grams (even if they have stopped seizing it's a good idea to load to something is on board when benzos wear off). Can also do IV Valproic acid 40 mg/kg. We typically never do IV phenytoin due to cardiovascular concerns/major issues with skin if IV infiltrates.

If they are still seizing after Keppra they need to be intubated if they haven't already and placed on a Versed infusion.

<u>3) How do I load ASMs?</u>

EPILEPSY

All of these ASMs are in IV form with a 1:1 PO:IV conversion (when in doubt can always ask pharmacist). **Always check a level 1 hour after loading the ASM for re-loading purposes (except for Keppra/Vimpat).**

DRUG	LOADING DOSE	TARGET LEVEL	RELOADING DOSE	MAINTENANCE DOSE
Phenytoin (Dilantin)	20 mg/kg (run at 25mg/min)	20	(Target - measured) x weight in kg	100 mg q8
Phenobarbital	20 mg/kg	40	(Target - measured) x weight in kg	3-5 mg/kg/day, divided BID
Valproic Acid (Depakote)	25 mg/kg 40mg/kg (status)	100	(Target - measured) x weight in kg x 0.2	30-60 mg/kg/day, divided TID (15-20 mg/kg/day for routine dosing)
Levetiracetam (Keppra)	3g	-	-	750-1500 mg BID
Lacosamide (Vimpat)	200 mg	-	-	100 mg BID
Fosphenytoin	20mg/kg, (max 1500mg) run at150mg/min	20	Target-measured) x weight in kg	4-6mg/kg/day

Re-loading based on post-load level:
(1) subtract (target level) - (measured level). This is how many additional **mg/kg** you want to give.
(2) multiply that by the patient's weight in kg. This is how many **total mg** you need to give.
(3) if Depakote, multiply the dose by 0.2

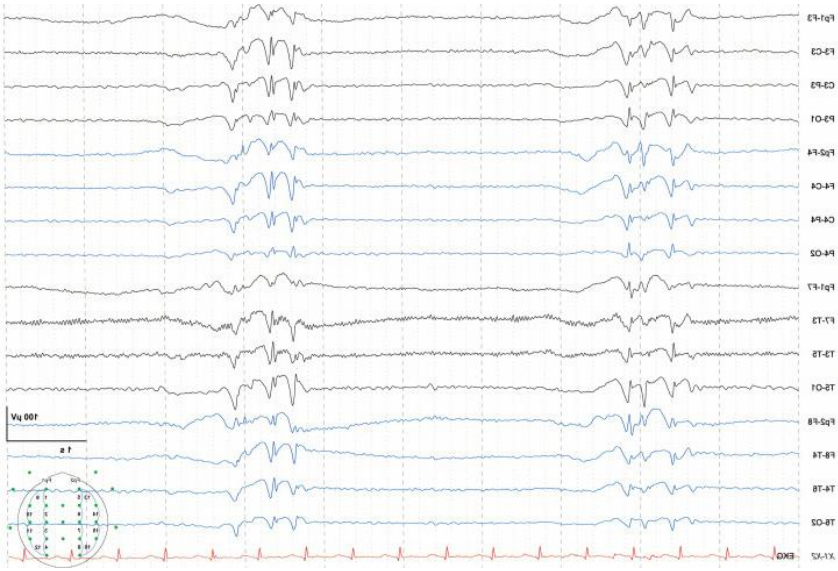
Example:
Dilantin goal level is 20, measured level is 12 and patient weighs 70 kg.
(target - measured) x weight = (20 -12) x 70 kg = 8 mg/kg x 70 kg = 560mg

4) What exactly is Burst Suppression?
For all status consults the goal will be seizure control, whether this means completely stopping seizures, or at least reducing them to a "safe" level. For some status cases, like those patients who progress through the pathway to intubation and sedation with versed, the goal will be to induce "burst suppression."
Burst Suppression refers to an EEG pattern produced by anesthetics (barbituates, propofol, versed) or by severe brain injury (a bad sign with the latter). This is felt to provide neuroprotection in status by reducing the cerebral metabolic rate, although the evidence behind this isn't great. Over night you may need to actively review the LTM of a patient in burst suppression (with help the senior and sometimes the Epilepsy Fellow). Your goal will be to make sure the EEG doesn't look too flat (too sedated) but that the bursts don't begin to coalesce. You will need to estimate the **Burst Suppression Ratio**. To do this:

1) Look at the LTM machine. The tracings displayed on the screen should represent 10 seconds of recording

2) Count the number of discrete bursts you see on the screen
3) If you see 1 burst, you have a ratio of burst to suppression or 1:10. 2 bursts you have 1:5 ***(shown below).*** 5 bursts would be 1:2 etc...
4) Generally want to aim somewhere around 1:4 – 1:2 is probably too light, 1:10 is getting too deep. Honestly though, as long as they aren't seizing that's usually good enough

Burst Suppression Example



From Rollnik, Jens. "Handbook of Clinical Neurology," 2019. We see two bursts surrounded by silence.

EEG reference material

FREQUENCIES

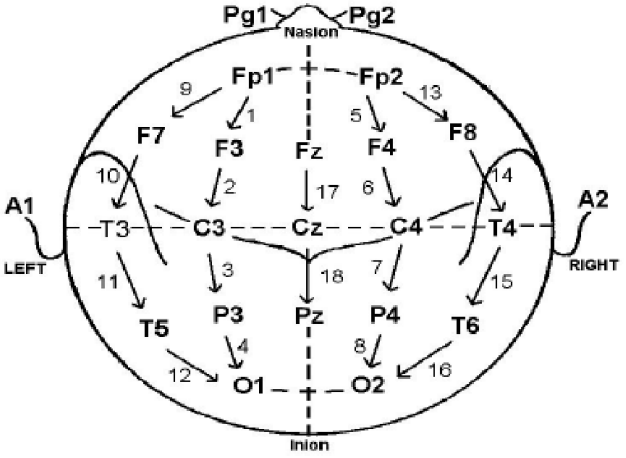
Delta: 0 – 4 Hz	Normal during slow wave sleep (stage III/IV); abnormal in various IRDA's
Theta: 4 – 7 Hz	

Alpha: 8 – 12 Hz	Normal predominant frequency during wakefulness
Beta: >12 Hz	Increased with benzodiazepine/barbiturate use (e.g. recent Ativan)

SLEEP STAGES

Wakefulness	Blinking; saccadic eye movements Posterior dominant rhythm (only present when eyes closed during wakefulness) EMG artifact
Stage I (drowsiness)	Dropout of alpha rhythm Roving eye movements Fonto-central theta, Vertex waves, POST's
Stage II sleep	Sleep spindles K-complexes
Stage III/IV sleep	>20% delta
REM sleep	Rapid saccades Absence of EMG artifact EEG desynchronization

Standard Montage: Longitudinal Bipolar (or "double banana")



1	Fp1-F3
2	F3- C3
3	C3- P3
4	P3- O1
5	Fp2-F4
6	F4- C4
7	C4- P4
8	P4- O2
9	Fp1-F7
10	F7- T3
11	T3- T5
12	T5- O1
13	Fp2-F8
14	F8- T4
15	T4- T6
16	T6- O2
17	Fz- Cz
18	Cz- Pz
19	LUC-A1
20	RLC-A2
21	EKG

EPILEPSY

Abnormal EEG findings

FINDING	DESCRIPTION	ASSOCIATION
Spike	Deflection of <70 ms duration	Epileptiform discharge, "electrode pop" (artifact, check lead)
Sharp	Deflection of 70-200 ms duration, typically has a field	Epileptiform discharge
Voltage Attenuation	<20 uV electrical activity (nml voltage 20-50 uV)	10% of normal patients have voltage attenuation
Slowing	Reduced frequency, either focal or generalized	Focal: mass lesion, stroke, bleed, resection cavity
		Generalized: diffuse cerebral dysfunction (encephalopathy, anoxic injury, systemic illness)
Burst-Suppression	Intermittent generalized high frequency activity interspersed with electrocerebral silence	High dose benzo/barb tx (e.g. status epilepticus), late-stage status epilepticus, anoxic injury
PLEDs	Periodic Lateralized Epileptiform Discharges	Epileptic potential, seen commonly after seizure, consider HSV
FIRDA	Frontal Intermittent Rhythmic Delta	Metabolic encephalopathy, *intracranial hypertension*, hyperventilation
TIRDA	Temporal IRDA	Temporal lobe epilepsy, Herples Simpex Virus, thalamic/BG lesions
OIRDA	Occipital IRDA	Seen usually in children
Triphasic Waves	Sharp upward deflection the sharp downward deflection then slow upward deflection; anterior-posterior lag	*Hepatic or renal dysfunction*, anoxic injury, hyponatremia, hypocalcemia, hypothyroidism, drug-induced (lithium, cefepime, CTX, naproxyn, levodopa, VPA, neuroleptic toxicity, serotonin syndrome), maple syrup urine disease, neuronal ceroid lipofuscinosis, Angelmann's *Note: CJD can be associated with 1Hz waves that resemble triphasic but actually have more of a diphasic morphology*
SIRPIDS	Stimulus-induced rhythmic, periodic, or ictal discharges	Common in critically ill patients (10-20%), not necessarily epileptic (if focal, then higher likelihood of epileptogenecity) but must correlate clinically, associated w/ poor prognosis d/t probability of neuronal injury

CRITERIA FOR ELECTROGRAPHIC SEIZURES

a. Epileptiform discharges averaging .2.5 Hz for 10 seconds (.25 discharges in 10 seconds), OR
b. Any pattern with definite evolution as defined above and lasting 10 seconds

Criteria for Electrographic status epilepticus

ESz for 10 continuous minutes
Or
for a total duration of 20% of any 60-minute period of recording

Criteria for Electroclinical Seizure (ECSz)
ECSz is defined as any EEG pattern with either:
a. Definite clinical correlate* time-locked to the pattern (of any duration)
OR
b. EEG AND clinical improvement with a parenteral (typically IV) antiseizure medication

Electroclinical Status Epilepticus (ECSE)
ECSE is defined as an electroclinical seizure for 10 continuous minutes
or
for a total duration of 20% of any 60-minute period of recording

Basic Electrographic Artifacts

ARTIFACT	DESCRIPTION	WHAT DO I DO?
Muscle artifacts		
Myogenic potentials or "muscle artifact" (e.g., chewing)	20-100 Hz high amplitude activity that correlates with muscle use	May use a 1-20Hz band pass filter to cancel any activity >20 Hz
Photomyogenic artifact	Sharp transients that co-occur w/ photic stimulation d/t simultaneous frontalis activation, more common w/ eyes closed	Nothing
Glossokinetic artifact	The tongue tip is negatively charged and can produce a low-med amplitude low frequency waveform observed in frontal electrodes	Recognize it with speech & feeding pattern w/ infants who are nursing
Ocular artifacts		
Lateral rectus spike	Usually present in F7 (left) or F8 (right) electrodes, this sharp transient represents a single motor unit potential from the LR & is followed by slower eye movement artifact in that direction	Nothing
"Blink" artifact	Like the tongue, the globe is a dipole (cornea is positive) and blinking produces a Bell's phenomenon which can be registered as a large amplitude slow wave that is maximal in frontal chains	Nothing
Slow, roving eye movements	Frontally predominant, very low frequency (~0.1 Hz) & low amplitude waveforms	Nothing
Cardiac artifacts		
EKG artifact	Intermittent, rhythmic sharp waves that align with EKG	Make sure you don't call them sharps
Pulse artifact	Intermittent, rhythmic delta waves that follow EKG depolarizations & occur over vessels	Confirm by reproducing the artifact through palpation of the affected electrode
Mechanical artifacts		

Electrode "pop"	Intermittent sharps (steep rise and shallow fall) that reflect poor adherence between electrode and skin, observe in 2 channels; distinguish from sharp by lack of clear field, isolation of single electrode in referential montage, and slower fall phase (sharps have abrupt up-and-down deflections)	Ask techs to fix electrode(s)
Perspiration artifact	Low amplitude, undulating waves (~0.5 Hz)	Nothing—They cannot be filtered out due to low frequency
Salt bridge	Low amplitude, much lower frequency than perspiration artifact, does not allow detection of cerebral activity	Can try to adjust electrode placement
External device artifact	Device-dependent: 60 Hz low amplitude rhythm that is attributed to nearby electrical circuits; "drip" artifact correlates with falling of electrically charged droplets from nearby IV pump; ventilator artifact has setting-dependent frequency but carries medium amplitude waveforms	Eliminate A/C current artifact with 60 Hz (notch) filter

HEADACHE
MIGRAINES

Clinical characteristics: recurrent attacks typically with prodrome (77% -- affective/vegetative symptoms), aura (25% -- most typically visual and develops gradually over several minutes), headache, and postdrome (drained/exhausted)...very common and impacts 12% of population...affects 17% of women and 6% of men each year…true cause unknown, but seems related to activation of the trigeminovascular system and sensitization (increased responsiveness) of neurons to noxious stimuli… Aura may result from cortical spreading depression.

Diagnosis:

- International Classification of Headache Disorders diagnostic criteria for migraine:
  1) At least 5 attacks fulfilling criteria 2-4
  2) Headache attacks lasting 4-72 hours (untreated)
  3) Headache has at least two of the following four characteristics
     - Unilateral
     - Pulsating
     - Moderate/Severe pain intensity
     - Aggravation by activity or causing avoidance of routine physical activity
  4) During headache at least one of the following:
     - Nausea and/or vomiting
     - Photophobia **and** phonophobia
  5) No better diagnosis exists

- Migraine with Aura:
  At least 2 attacks with:
  - 1+ reversible aura symptoms (visual, sensory, speech/language, motor, brainstem, retinal)
  - At least three of the following: one aura spreads gradually over 5 min, 2+ auras occur in succession, each aura lasts 5-60 min, one aura is unilateral, one aura is positive (scintillations, paresthesias), aura is accompanied or followed within 1 hr of headache

-Chronic Migraine: 15 or more headache days per month for more than three months with features of migraine headache present at least 8 days per month.

Treatment

Acute treatment: every patient with migraines should be provided with a treatment plan to abort acute migraines. Features to consider when crafting a plan are frequency of severe vs less severe headaches, presence of significant nausea/vomiting, duration of migraines and need for repeated doses of rescue medication, timing of medication administration.

Key Point: Patients will often be able to differentiate between a severe headache responsive only to Triptans and less severe headaches that are responsive to NSAIDs/Tylenol so a two-pronged approach can be used.

Interventions with class A evidence:

1. **Acetaminophen 1000mg for mild-moderate migraines**
2. **NSAIDs (aspirin 500mg, diclofenac 50 or 100mg, ibuprofen 200 or 400mg, naproxen 500 or 550mg) for mild-moderate**
3. **Triptans – migraine specific and most effective for moderate-severe migraines**
   a. Mechanism: agonists for serotonin 5-HT1b and 5-HT1D receptors at blood vessel and nerve endings in brain –> promotes vasoconstriction of cerebral blood vessels, inhibits

neurogenic inflammation around blood vessels, reduces neuronal activity within trigeminovascular system. Need to give early on in migraine

b. Contraindications: migraine with brainstem aura, hemiplegic migraine, stroke, CAD, uncontrolled HTN, use of DHT within the past 24 hours

c. Side effects: fatigue, dizziness, chest discomfort, somnolence, nausea.

d. List of triptans:

i. Sumatriptan (Imitrex): short acting, faster onset, 50-100 mg PO (but prefer larger dose). Can repeat dose 2 hours after headache onset but no more than 2 doses in 24 hours. Comes in intranasal spray (10 mg), intranasal solution (20 mg) and subq (6 mg) if nausea is severe.

ii. Rizatriptan (Maxalt): short acting, fast onset, 5-10 mg PO (prefer larger dose). Can repeat in 2 hours, but no more than 2 doses in a 24 hour period. Decrease dose if on propranolol. **Consider as first-line triptan**

iii. Frovatriptan (Frova): long acting, 2.5 mg PO. Can repeat at 2 hours, but no more than 2 doses in 24 hours.

iv. Naratriptan (Amerge): long acting, 2.5 mg PO, **can repeat at 4 hours,** but no more than 2 doses in 24 hour period**.**

Naratriptan and Frovatriptan are **Not Fast** (long-acting triptans) and can be used as prophylaxis for menstrual migraines.

v. If one triptan fails - try another! Patients may sometimes need to be tried on different triptans before finding one that works. If patients have significant nausea, consider a non-oral route such as intranasal sumatriptan. Try combining with tylenol or an NSAID for better pain control

4. Lasmiditan: selective 5HT1F agonists that do not cause vasoconstriction, and thus can be given to patients with contraindications to triptans. Dose: 50-100mg, with no benefit to repeated doses. Side effects: CNS depressant so can cause sedation, dizziness, fatigue. **Avoid driving for 8 hours after use**

5. Gepants: ubrogepant (Ubrelvy) and rimegepant (Nurtec) are oral CGRP antagonists approved for abortive therapy. Theoretically no risk of vasoconstriction although animal studies have shown worsening cerebral infarct risk. **No risk of medication overuse headache**

a. Ubrogepant: 50-100mg, can repeat after 2 hours. Side effects: nausea, somnolence, dry mouth. Studied at 8 doses per month.

b. Rimgepant: 75mg, no benefit to repeat dose. Side effects: nausea, hypersensitivity. Studied at 15 doses per month. Can also be used as a preventative with every other day dosing (see below)

6. Neuromodulation devices: external trigeminal stimulation, single-pulse magnetic stimulation, non-invasive vagus nerve stimulation, remote electrical neuromodulation. Limited by cost. Side effects are mild so consider for patients with intolerance to other therapy. Samples are available in the clinic to show patients.

Question: Are Triptans safe with SSRI's?

Answer: You will often receive an alert when prescribing a triptan in a patient on an SSRI due to risk of serotonin syndrome stemming from a 2006 FDA report based on 9 cases. A more in-depth review showed that only 10 cases met criteria for serotonin syndrome and incidence is very low – less than 0.03%. In this setting you can give patients the data and counsel on what to look out for when prescribing this combo.

There is a "Suspected Migraine Treatment" Pathway. Please refer ED providers to this pathway in Dorsata/PennPathways.

Anti-emetics

- Reglan, Compazine, and Zofran can all be used in combination with the above options when there is a component of nausea. Look for oral dissolving tablets (ODT) as these can reach the blood stream quickly and are easier to take with significant nausea. Counsel patients to not take these more frequently than prescribed due to risk of QT prolongation.

When the acute treatment plan fails:

- Pred taper: 40 mg x 2 days, 30 mg x 2 days, 20 mg x 2 days, 10mg x 2 days.
- Valproic acid (ensure not pregnant): 500 mg BID x 3-5 days
- Pregnant patients: occipital nerve blocks
- Symptom Management Service: provides acute symptom management for patients with chronic conditions who may need IV medications. Located in PCAM 3 West, open M-F 9am-7pm by appointment only. Patients are referred by Epic messaging "PCAM Symptom Management Clinic". They will take care of all orders but you can request a specific cocktail. Medications to consider include IV toradol, IV reglan with benadryl (to prevent dystonic reactions), IV fluids. Can also add IV magnesium as second line. an IV valproic acid 15mg/kg (max 1g) followed by oral valproic acid, or IV decadron 10mg with a steroid taper are third line options. Goal is to keep patients from needing ED visits. See "Headache in the ED" section for further information.

<u>Preventive treatment:</u>

(NOTE: for treatment of chronic migraines please see "Approach to Chronic Headaches" section below)

1) Lifestyle modifications

- Aerobic exercise – 150 minutes per week – can reduce headache frequency
- Headache diary to account for triggers
- Caffeine: regular caffeine use is a risk factor for developing frequent headaches; try cessation for 2-3 months to determine if this helps.
- Sleep: poor sleep is common in migraine patients. Assess for OSA risk factors and refer for sleep study if needed.

2) Nonpharmacological therapies

- Acupuncture (although sham needling likely as effective)
- Behavioral therapy: consider when patient stressors are triggers for migraines. Patients can go to AAPB.org to look up a practitioner near them.
- Headache physical therapy - ask about teeth grinding specifically as this can be targeted with physical therapy. Good Shepherd has therapists specialized in headache and facial pain that you can direct patients to

3) Indications for daily medication

- Three or more mod/severe headache days per month causing functional impairment
- At least 6-8 headache days per month even if acute medications effective
- Bothersome symptoms with infrequent attacks (hemiplegic migraines)
- Patient at risk for developing medication overuse headache

Daily medications:

First line options: 50% will see 50% reduction in headaches

Beta Blockers	Propranolol: 40 mg daily divided BID, can titrate up to 160 mg per day Metolprolol: 50 mg daily divided BID, can titrate up to 200 mg daily	Consider in patients with co-morbid hypertension *Avoid in patients over 60 or smokers (increased risk of stroke/CV event), asthma,

	Nadolol: 20 mg once a day, can titrate up to 240 mg daily Atenolol: 25 mg daily, can titrate up to 100 mg daily	erectile dysfunction, peripheral vascular disease, bradycardia/low BP, diabetes (masks hypoglycemia)
Tricyclic antidepressants	Amitriptyline: 10 mg at bedtime, titrate up to 50 mg at bedtime in 10 mg/week steps Nortriptyline: 10-25 mg at bedtime, can titrate up in 10-25 mg/week steps to goal of 75-100 mg/day	consider in patients with insomnia or neuropathic pain *Can cause dry mouth, constipation, tachycardia, orthostasis, **weight gain**, urinary retention (anticholinergic side effects) *poor choice for older or overweight individuals *nortriptyline tolerated better than amitriptyline due to less sedation
Topiramate	Start at 25 mg at night, increase to 25 mg BID after one week then add 25 mg per week until at 50 mg BID. Can push up to 200 mg/day for migraine purposes	Consider with co-morbid obesity, seizures, or concern for IIH *avoid in patients with kidney stones or patients who may become pregnant *monitor for metabolic acidosis *can cause paresthesias, fatigue, anorexia, cognitive fog, taste perversion *can also use Zonisamide *NOTE: can decrease serum concentrations of estrogen OCPs leading to contraceptive failure!! Happens at doses of 200 mg/day or greater typical
Magnesium/Riboflavin	Magnesium: start at 400mg qd, can increase to 600mg Riboflavin: 400mg qd	Mag- can cause diarrhea Riboflavin- can cause orange discoloration of urine

Start low and go slow until patient has a clinical response or maximum tolerated dose is achieved. An adequate trial will take at least 6 weeks, but patients may continue to have a response up to 3-6 months.
Note: valproic acid has class A evidence as a preventative but given side effects with chronic use tends not be used first line

Second line:

1. Try a different agent on the above list if able
2. **Venlafaxine**: try in patients with anxiety/panic disorder
    a. Start at 37.5 mg daily for 3 days then increase by 75 mg increments to target of 75 to 150 mg daily
    *evidence base is not as strong as first line agents

3. **Verapamil**: consider in older patients with HTN, Raynaud's phenomena, or prolonged migraine aura (hemiplegic, brainstem)
    a. Start at 120 mg Daily ER, can increase every 1-2 weeks up to 360 mg per day in 2-3 divided doses
    *monitor for bradycardia/hypotension
4. **CGRP antagonists**: antibodies targeting calcitonin related peptide as this is felt to have a role in mediating the trigeminovascular pathway
    a. Patients will typically need to fail several of the above medications before proceeding with this class, or have contraindications – partly depends on insurance
    b. Consider side effects when prescribing (I.e. avoid Aimovig if someone already has issues with constipation)
5. Other medications to consider: memantine 10mg bid, ACE inhibitors (lisinopril, candesartan)

CGRP Antagonists					
Agent	**Brand name**	**Target**	**Dosing**	**Side effects**	**Efficacy data**
Erenumab	Aimovig	Inhibits CGRP receptor	Subq: 70 mg monthly, can increase to 140 mg per month	Site reaction, hypertension, constipation	# migraine days/month reduced by 3.2 vs 1.8 in placebo
Fremanezumab	Ajovy	Binds to CGRP ligand	Subq: 225 mg per month or 675 mg every 3 months	Site reaction	50% reduction in migraine days in 50% of patients vs 28% for placebo
Galcanezumab	Emgality	Binds to CGRP ligand	Subq: 240 mg loading dose, then 120 mg per month	Site reactions	# migraine days/month reduced by 4.7 vs. 2.8 for placebo
Rimegepant	Nurtec	CGRP receptor antagonist	Acute: 75mg PO (max 75mg/24 hours) Prevention: 75mg PO every other day	GI symptoms	# migraine days/month reduced by 4.3 vs 3.5 for placebo
Atogepant	Qulipta	CGRP receptor antagonist	Prevention: 10, 30, or 60mg daily	**Weight loss,** constipation, nausea	56-61% with 50% reduction in migraines compared to 29% of patients in placebo arm

Prescribe by sending to PCAM pharmacy - they will start the prior authorization process (if needed)

Discontinuation of preventative therapy: generally want to see 3-6 months of **headache freedom** before doing a slow taper.

HEADACHE

Procedures:

- Botox Injections
    - Data from two large RTCs (PREEMPT 1 and PREEMPT 2) showed that botox was superior to placebo in reducing headache days in chronic migraine (≧15 HA days/month). It is considered second line due to its high cost and requirements of insurance companies that agents from several classes must have been trialed first.
    - Administered every 12 weeks via injections into 31 total sites around the head/cervical musculature
    - How to order?
        1) Under "Smart Sets" in the Plan section, search for "Neuro Botox HA Referral Smart Set"
        2) Select appropriate diagnosis
        3) Add the Neuro Botox HA History to your note by clicking Add Now and then fill out all the required information
        4) Add the "Consult to Neuro Botox for Headache" to your orders for the visit

    NOTE: Give at least 2-3 sets of injections before declaring Botox a success or failure

Completing a botox visit

1. In the visit note, use Dr. Rubenstein's ".botoxvisit" SmartPhrase. If it is a follow-up patient, make sure to document how their headaches responded to their last botox, and the date of their last botox
2. Setting up the botox (ask the supervising attending to help you the first few times):
    a. Mix a little more than 4mL of saline into the botox vial. Leave the longer needle in the vial as you will use this to draw up your syringes
    b. Swirl the botox vial to mix the powder at the bottom with the saline. Do not invert the vial as you do not want liquid sticking to the cap.
    c. Draw up 1cc into each of the 4 syringes. Put the smaller needle and cap on the syringe. While holding the plunger, vertically shake the syringe so that the air bubble migrates to the top. Push the plunger to eject the empty air out of the syringe.
3. Perform botox injections (31 sites)
4. After the injections are completed, find the "Neruo HA botox injection visit" SmartSet. Sign the SmartSet
5. Go to the "Med Management" tab in the plan tab. Hit the botox you just ordered and click "Administer". Fill in the lot number
6. The botox note should have been added to your initial visit note. F2 through it and make sure to write the botox vial expiration date at the bottom
7. Send chart to supervising attending

- Occipital Nerve Blocks: see section on this later in chapter under chronic headache therapies.

Evidence Base and Dosing Ranges for Preventative Migraine Therapies

Medication	Target dosing[9]	Level of evidence per 2012 AAN/AHS guidelines[10]	Notes
Divalproex sodium	250-500 mg 2 times a day or 500-1000 mg delayed release once daily	A	May cause thrombocytopenia or hepatotoxicity; monitoring is required; contraindicated during pregnancy; use limited by side effect burden despite efficacy
Topiramate	100 mg once daily or 50 mg 2 times a day	A	May cause weight loss, which some patients find beneficial; contraindicated in patients with nephrolithiasis
Metoprolol	50 mg 2 times a day	A	Unlikely to worsen asthma (highly cardioselective)
Propranolol	60 mg once daily or 2 times a day	A	Contraindicated in people with asthma; evidence that beta-blockers worsen depression has been challenged in recent years
Eptinezumab	100-300 mg IV every 3 months	N/A	Faster onset because of IV administration
Erenumab	70 mg or 140 mg subcutaneous monthly	N/A	Constipation, hypertension, hypersensitivity reaction
Fremanezumab	225 mg subcutaneous monthly (most common) or 675 mg subcutaneous every 3 months	N/A	
Galcanezumab	240 mg subcutaneous loading dose, then 120 mg subcutaneous monthly	N/A	
OnabotulinumtoxinA	155 units subcutaneous monthly	A	Lack of systemic side effects and drug interactions makes this a high-priority option for patients with chronic migraine
Amitriptyline	50 mg nightly	B	Generally better tolerated when started at lower doses and increased slowly
Venlafaxine	75-225 mg extended release once daily	B	May worsen headaches in some patients; withdrawal syndrome can be prolonged and bothersome

Rebecca Burch. "Preventive Migraine Therapy." Continuum June 2021.

Treatment of migraines in pregnant/breastfeeding patients

Pregnancy

Acute therapy: This is challenging. Tylenol is always a safe option and Reglan is also considered safe. NSAIDs can be used in the first/second trimester but need to be avoided in the third trimester as they can close the ductus arteriosis. Triptans are likely also safe. Nerve blocks with lidocaine or ropivicaine is also considered safe and can be used for both acute and preventative treatment.

Preventative therapy: Migraine without aura generally improves in pregnancy, but less so for migraine with aura). This is very challenging. **Nerve blocks can still be used and may be the safest option. Propranolol** may be the drug of choice. Memantine, coenzyme Q10, and cyclobenzarpine should be considered second-line. Other second line medications such as TCAs, SNRIs, or CCBs should be avoided unless necessary.. Further research is required on CGRP antagonists and botox injections although are likely safe. **Avoid topiramate and ACEi/ARBs.**

Breast-feeding

Acute therapy: preferred agents are acetaminophen, lidocaine injections, and NSAIDs. Second-line options include diphenhydramine, metoclopramide, ondansetron, triptans, and prednisone. Avoid aspirin, opiates, and ergot derivatives.

Preventative therapy: preferred agents include verapamil, propranolol, magnesium, and valproic acid. Amitriptyline is second-line. The safety of cGRP antagonists and botox have not been studied.

Migraine subtypes:

1) Migraine with brainstem aura ("basilar migraine")

- Diagnosed in patients with migraine and aura with at least two of: dysarthria, vertigo, tinnitus, hyperacusis, diplopia, ataxia, GCS less than 13
- Presentation should prompt MRI/MRA or CTA
- Unclear prevalence due to varying diagnostic criteria – more common in women, age of onset usually between 7 to 20 years
- If sure about diagnosis, must avoid beta blockers, triptans, ergots
- Verapamil or topiramate used for prevention

2) Hemiplegic migraine

- Very rare, onset in teen years, more likely in women
- Motor aura with unilateral weakness is hallmark. Unilateral features can switch sides between or during attacks
- Often will run in families – CACNA1A, ATP1A2, SCN1A mutations seen
- Avoid triptans/Ergots. Some avoid Beta blockers as well (prevent compensatory vasodilatory capacitance of cerebral vessels
- Acute management with same meds as normal (avoiding the above); steroids for severe attacks. Preventive therapy with Verapamil ER or diamox.

3) Retinal migraine

- Rare, repeated attacks of monocular scotomata or blindness lasting less than 1 hour, often followed by a headache.
- Irreversible vision loss can occur – migraineous infarcts have been raised as the etiology. Due to this many will treat with Verapamil for prevention and avoid triptans, ergots, and beta blockers due to risk of ischemia.

4) Menstrual migraines

- Migraines that occur in close relationship with menses (declining estrogen levels are an important trigger.
- Can use NSAIDs/Triptans for abortive therapy, but can also start standing Naproxen around menses or scheduled dosing of frovatriptan 2.5 mg daily/BID for two days before menses and continued for 5 days.

5) Migraine without Aura: see diagnostic criteria above

TENSION-TYPE HEADACHE

Clinical characteristics: most common headache type. Characterized by mild/moderate intensity pain, bilateral in nature with dull feeling. One-year prevalence roughly 60%. Peaks in 4th decade but often occurs in older individuals.

Pathophysiology: myofascial nociceptors become sensitized leading to normally innocuous stimuli to be interpreted as pain (intensity and frequency of tension type headaches correlates with pericranial muscle tenderness). Continuous input from peripheral myofascial structures can lead to central sensitization which leads to chronic pain.

Diagnostic Criteria ICHD-3 (further differentiated by infrequent, frequent episodic and chronic)**:**
At least 10 episodes:

- Lasting 30min-7days

- At least two of the following: bilateral, pressing/tightening, mild-moderate intensity, no worse with routine activity
- Absence of nausea/vomiting
- Can have photophobia OR phonophobia but not both

Can break down into infrequent episodic (less than 1 headache day per month), frequent episodic (1-14 headache days per month), or chronic (>15 headache days per month).

Treatment

Acute treatment:

-General principles

- Unlike in migraines, no evidence that delaying acute treatment after a tension headache starts leads to treatment failure
- Intensity of headache does not predict treatment failure
- Must avoid medication overuse – limit NSAIDs to 15 days per month, and anything containing butalbital to 3 or fewer days per month (higher risk of medication overuse headache)
- If acute therapy is not working make sure the diagnosis of tension type headache is correct (exclude migraine or secondary headache – mass, etc)

-Medications

1) **NSAIDs:** Options include ibuprofen 400-600mg, naproxen 220-550mg, diclofenac 25-100mg, or aspirin 500-650mg
    - least likely to cause medication overuse headache
2) **Acetaminophen (1000 mg)**
3) **Combination analgesics with caffeine 130mg:** more effective than simple analgesics alone but more likely to cause side effects. Prescribe if simple analgesics ineffective
4) **Severe attacks:** IV toradol 15-30mg + IV reglan 10mg

NOTE: *DO NOT prescribe butalbital or codeine containing medications* unless absolutely nothing else has worked! They are high risk for overuse leading to worsening headaches. Can even have withdrawal seizures if take way too much butalbital and stop cold turkey.

Preventive treatment: indicated with frequent tension type headaches – approaching 10 or more headaches per month.

1) **Non pharmacological treatment**: worth a try in patients with significant stress/anxiety, excessive use of acute medications, or those with medication side effects
    - Biofeedback therapy: Look up practitioners at AAPB.org
      *Decent data suggests that biofeedback is more effective than other non-pharm techniques like relaxation therapy and can be combined effectively with daily medication
2) **Daily medications**

    Tricyclic antidepressants **Highest level of evidence**

    Reduced frequency by 5 headaches/month (although baseline was 21 headaches/month in meta analysis)

    See migraine section for titration of TCAs

    Mirtazapine and Venlafaxine **Not first line**

    *Limited data, positive results obtained in small studies – more expensive than the TCA's

    NOTE: SSRIs are not effective for TTH in the absence of co-morbid depression

    Topiramate or gabapentin **Not first line**

    *Positive results seen in small study with 51 patients
3) **Injections:** trigger point or botox, both of uncertain benefit

HEADACHE

MEDICATION OVERUSE HEADACHE

Thought to be withdrawal headache from chronic analgesia use (opiates and barbiturates particularly high risk)

Diagnosis: Headache occurring on 15 or more days/month in a patient with a pre-existing primary headache and developing as a consequence of regular overuse of acute headache medications (on 10 or more or 15 or more days/month depending on the medication) for > 3 months.

Acetaminophen, Aspirin, NSAIDs for >15 days per month
Ergotamine, triptans, opioids, combination analgesics > 10 days per month

Treatment:

- Avoid entirely by providing strict guidelines to patients for correct acute medication use and instituting preventive therapies when indicated. Many patients (and physicians) DO NOT know that this is an issue.
- Counsel patients to use fast acting analgesia <2x/week
- Headaches should revert back to episodic phase with withdrawal of overused medications.
- Strategies to wean overuse of analgesic medications:
    - Switch to alternative symptomatic therapy
    - Continue overused medication during initial treatment
    - Add additional temporary medication (consider naproxen, tizanidine + NSAID, or steroids), although bridge therapy does not have great data
    - Discontinue overused medication before starting preventative medication
- Start appropriate preventative medication or change a previously ineffective preventative, although preventative not always needed if headache burden was mild prior to analgesic overuse

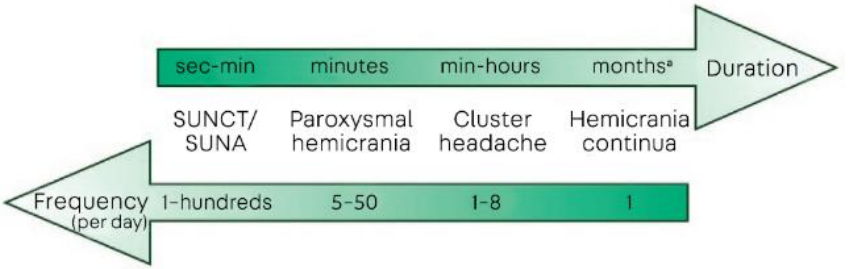
TRIGEMINAL AUTONOMIC CEPHALGIAS

Headaches that are ipsilateral, typically in the V1 distribution, ipsilateral parasympathetic autonomic features (injection, lacrimation, congestion/rhinorrhea, ptosis, miosis, eyelid edema) due to trigeminal - parasympathetic reflex. Workup often includes MRI to assess for secondary causes. A brief summary of TACs here:

HEADACHE

TABLE 9-1 Comparison of the Trigeminal Autonomic Cephalalgias

	Cluster Headache[1]	Paroxysmal Hemicrania[2]	SUNCT/SUNA[3]	Hemicrania Continua[4]
Ratio of female to male	1:3	Slightly more female	1:1.5	2:1
Pain				
Quality	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Sharp, stabbing, throbbing	Baseline: aching; exacerbations: sharp, stabbing, throbbing
Severity	Very severe	Very severe	Severe	Baseline: mild to moderate; exacerbations: moderate to severe
Attacks				
Frequency (per day)	1-8[a]	5-50	1 to hundreds	Constant
Duration (minutes)	15-180	2-30	0.01-10[b]	Baseline: 3 months or more; exacerbations: 30 minutes to 3 days
Ratio of episodic to chronic	90:10	35:65	10:90	15:85[c]
Associated features				
Restlessness	90%	80%	65%	70%
Circadian periodicity	82%[5]	Rare	Rare	Rare
Triggers				
Alcohol	Yes	Yes	No	Yes
Nitroglycerin	Yes	Yes	No	Rare
Neck movements	No	Yes	Yes	No
Cutaneous	No	No	Yes	No
Treatment response				
Oxygen	70%	No effect	No effect	No effect
Sumatriptan 6 mg subcutaneous	90%	20%	Rare effect	No effect
Indomethacin	Rare effect	100%	No effect	100%



Both figures from Mark Burish. "Cluster Headache and Other Trigeminal Autonomic Cephalgias." Continuum August 2018.

Cluster Headache:

- Majority of cases of TACs. Severe, one-sided excruciating headache with at least one ipsilateral autonomic sign (tearing/rhinorrhea/injection/ptosis/meiosis); lasting 15-180 minutes, 0.5-8 per day, usually in periods of months with months-years of remission
- Onset age 20-40, male predominance. Associated with **agitation**
- NOTE: with cluster headaches patients will often get clusters of their cluster headaches – e.g they will have headaches for several days, then these go away only to flare up again several months down the road.
- Secondary causes: vascular (carotid dissection, carotid-cavernous fistula, CVST) or non-vascular (glaucoma, sinusitis, trigeminal nerve root compression, tumors). **Recommended to obtain MRI with contrast and vessel imaging if concerned for cluster headaches**

Treatment:

- Acute headache: 100% oxygen via nonrebreather or subq sumatriptan, then a transitional medication is started as a bridge to a longer lasting preventive therapy.
- Transitional therapy: suboccipital steroid injections or oral steroids (prednisone 100mg x 5 days followed by 20mg taper every 3 days)
- Preventative therapy

- Verapamil: start at 40-80mg tid, then titrate daily dose of 400mg divided TID with attention paid to bradycardia and lengthened PR interval at higher doses (EKG monitoring advised with dose increases)
- Topiramate, lithium, and galcanezumab used as second/third line.
- Melatonin can be used as an adjunctive medication

*Once the patient is headache free for several weeks, the preventative medication can be down titrated and discontinued as long as the patient has a history of well spaced out clusters.

Paroxysmal Hemicrania

Diagnostic criteria: 20 attacks of severe, unilateral pain lasting 2-30 minutes, >5/day with autonomic symptoms or agitation, with a complete response to indomethacin

Treatment:

- Indomethacin: titrate up from 25 mg TID for 3 days, then escalate to 50mg tid for 3-10 days before considering further escalation. Max dose: 225mg/day. Prescribe PPI/H2 blocker at same time. Then titrate down to find smallest effective dose.
- Verapamil, topiramate second/third line

SUNHA (previously SUNCT/SUNA)

Diagnostic criteria: 20 attacks of severe unilateral pain lasting 1-600 seconds, with atleast one ipsilateral autonomic symptom, occurring atleast once a day

Treatment:

- Lamotrigine: titrate to dose of 100-200 mg per day
- Topiramate, gabapentin, carbamazepine, oxcarb, duloxetine other options
- Consider surgery if found to have vascular loop compression of trigeminal nerve

Hemicrania Continua:

Persistent (>3 months) unilateral pain with ipsilateral autonomic symptoms, exacerbated by movement, with response to indomethacin

Treatment:

- Indomethacin: see dosing for paroxysmal hemicrania
- COX inhibitors, melatonin, gabapentin, verapamil, topiramate, occipital nerve blocks, botox also used.

Trigeminal Neuralgia:

Paroxysmal, severe, shock-like unilateral facial pain confined to 1 or more trigeminal dermatome; triggered by stimulation - cold, talking, chewing

Often episodic at onset then evolves into chronic pain

Can be idiopathic or secondary: compressive (mass, vascular loop), inflammatory (MS)

Workup: imaging - MRI/MRA - to assess for causes of secondary trigeminal neuralgia

Treatment

Carbamazepine, oxcarbazepine > baclofen, lamotrigine, phenytoin

Surgical: microvascular decompression, rhizotomy, gamma knife

APPROACH TO CHRONIC DAILY HEADACHES

Chronic daily headaches refers to a cluster of related diagnoses characterized by frequent, near daily headaches…When you hit 15 headache days per month you are dealing with a chronic daily headache…Prevalence is about 4 percent worldwide and women are affected 2-3x more than men…After ruling out red flags that should push you to perform neuroimaging, management of the chronic daily headache hinges on separating the patient into **one of three categories – chronic migraine, chronic tension type headache, or medication overuse headache**…sometimes,

however, it is difficult to make the distinction and empiric preventative therapy is started to reduce headache frequency so a pattern/headache phenotype can then emerge.

Bottom Line: Treatment should be targeted to the specific underlying headache type, whether with or without a component of medication overuse headache. The TCAs are a good go-to first line for chronic daily headaches regardless of the underlying headache type. Topiramate is a good second choice if the patient cannot tolerate the TCA. Non-pill options should be considered, like nerve blocks and Botox.

Treatment commonalities

- Set realistic goals from the start (headaches will not be eradicated immediately; goal should be to see improvement in frequency/severity/disability from one appointment to the next)
- Minimize the use of abortive medications (see medication overuse headache above)
- Identify and treat relevant co-morbid conditions (like OSA)

OTHER THERAPIES

Occipital nerve blocks

- Useful in a variety of headache syndromes – occipital neuralgia, chronic migraines, chronic tension type headaches, status migrainosus
- **How to order:** Place order for Trigger Point Injections and then patient can call in to the Neurology office to schedule, or you can perform it on resident clinic day with an attending who can supervise (headache attending, Dr. Price, Dr. Rubenstein) - make sure to email the attending in question beforehand to make sure this is okay!
- **How to perform occipital nerve blocks:**

1) **Necessary materials to have in room** (assuming you are injecting one greater occipital nerve and one lesser occipital nerve on each side – 4 injections in total):
-Syringe
5 cc syringe x 2(Dr. Kaiser) or 1 cc syringe x 4 (Drs. Rubenstein/Price)
-Needle: 25 to 27 gauge 1" to 1.25" (would confirm with attending)
-1% lidocaine
-Methylprednisolone (40 mg/ml) (note that not all attendings use steroids)
-alcohol swabs to clean skin
-Gauze to dab away drops of blood
-Not a sterile procedure, so can use gloves from clinic room

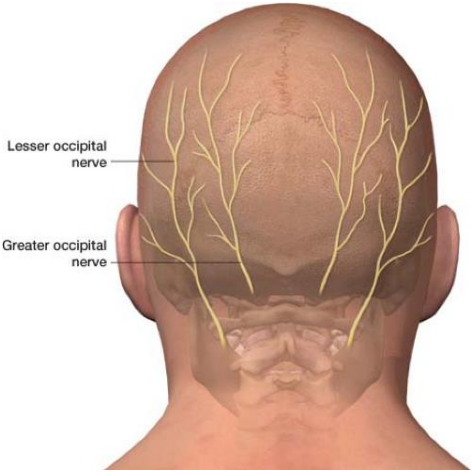
2) **Consent patient:** Relevant potential risks include bleeding and infection. Use EPIC consent form for nerve blocks/trigger point injections.

3) **Performing procedure:**

1) Find your landmarks
   a. External occipital protuberance -- raised area in the midline of the occipital bone where posterior wall meets base of skull
   b. Mastoid process -- posterior to external acoustic meatus (that boney bump behind your ear)
   c. To locate your injection sites draw an imaginary line between the external occipital protuberance and the mastoid process
      i. Greater occipital nerve is 2/3 along line (closer to occiput)
      ii. Lesser occipital nerve is 1/3 along line (closer to mastoid process)
      iii. NOTE: that you can modify injections sites based on areas of maximal tenderness when you are palpating, patients may not follow these exact rules
2) Prepare the injection sites

a. Pushing hair to the side, scrub the areas with alcohol swabs until clean

3) Prepare for injection
   a. If using 1 cc needles (Rubenstein/Price): Fill up each syringe with 0.8 cc Lidocaine and 0.2 cc steroids
   b. If using 5 cc needles (Kaiser): Fill up each syringe with 4.5 cc Lidocaine +/- 0.5 cc steroids
4) Greater occipital nerve block
   a. Insert the needle at an upwards angle (30ish degrees) and slightly lateral angle until you hit the periosteum. Pull back to ensure no blood flush. Then inject a full 1 cc or 3.5 cc depending on attending (warn the patient they may feel a pressure like sensation)
5) Lesser occipital nerve block
   a. Insert the needle at an upwards angle (30ish degrees) and slight medial angle until you hit the periosteum. Pull back to ensure no blood flush. Then inject a full 1 cc or 1.5 cc depending on attending (warn the patient they may feel a pressure like sensation)
6) Charting after the procedure:
   a. Attending may have you do the following:
      i. Open up "Neuro Trigger Point Injection" smart set
      ii. Choose correct diagnosis
      iii. Select procedure based on number of trigger point injections
      iv. Order medications you used during the procedure (they should be listed as clinic administered medications)
      v. Fill out procedure note (can use Dr. Ozudogru's .SOMINORPROCEDURE smartphrase)



Occipital nerve block landmarks

PT for cervicogenic headaches

- Think about this when there is clinical/imaging evidence of disorder w/in cervical spine or soft tissues of the neck leading to referred pain to the cranium (headache). This can be demonstrated by temporal relationship (headaches starting after neck trauma), reduced cervical range of motion with worsening headache, or improvement of headache after

diagnostic blockade of cervical structure/nerve supply. These headaches are typically unilateral, may also be accompanied by radicular pain

- **How to order:** Place PT order, specify reason as headache program, and have them call 215-294-9216 to schedule a headache evaluation with Ali Ladak or Christina Pettet (both at 3737 Market Street). Can use Dr. Rubenstein's .PTRECSTMD smartphrase.
  - They will evaluate cervical ROM, mobility, and provoking maneuvers in context of patient's headache and prescribe ROM, strengthening exercises, soft tissue mobilization, postural re-education, biofeedback and more!
- **Can this be useful in patients with Migraines?** Yes, some migraine patients have features that overlap with cervicogenic headaches, and there is data suggesting that combining parts of what PT's can offer compliments other preventive strategies and reduces headache days and disabilities.

HEADACHE IN THE ED

DIFFERENTIAL DIAGNOSIS

1) Meningitis: diffuse, photo/phono, meningismus, N/V, fever, malaise, irritability
2) Encephalitis: like meningitis, plus altered mental status, seizures, focal features
3) Subarachnoid hemorrhage: sudden-onset, WHOL, 10/10, meningismus
4) Pseudotumor cerebri: diffuse, photo, tinnitus, transient visual obscurations, vision loss, VI palsy + wt gain/Vit A/meds
5) Carotid dissection: periorbital/auricular throbbing (carotidynia), Horner's, TMB, focal features
6) Temporal arteritis: achy, jaw claudication, myalgias, ESR > (age/2 + 10), wt loss. If concern for ophthalmic involvement (i.e. sudden, painless vision loss), start high-dose steroids (IVMP 500-1000mg daily) immediately. If no vision symptoms, start prednisone 40-60mg daily.
7) Hypertensive encephalopathy: frontal/occipital, throbbing, +/- confusion
8) Venous sinus thrombosis: diffuse or focal, seizure, meningismus
9) Optic neuritis/myositis: painful eye movements +/- vision loss, F>M
10) Migraine: moderate unilateral, F>M, pulsatile, photo/phono, n/v, scintillating scotomas, fortification spectra, + family history, + menstrual, + triggers. *Subtypes*: *common* (no aura, 50%), *classic* (aura, 50%), *complicated* (focal features, <5%), *retinal* (monocular vision loss), *vertiginous*, *acephalgic* (aura without headache)
11) Tension-type: bilateral, pressure, "hatband", shoulder/neck tightness
12) Cluster: severe unilateral lasting 15-180 minutes, M>F, 2-3 times per day x wks-mths, photo/phono, autonomic features (Horner's, tearing, rhinorrhea)
13) Paroxysmal Hemicrania: severe unilateral lasting 2-30 minutes, F>M, 5 times per day x wks-mths, photo/phono, autonomic features (Horner's, tearing, rhinorrhea), indomethacin-reponsive
14) SUNCT syndrome: "short-lasting (less than 2 minutes), *u*nilateral, *n*euralgiform, *c*onjunctival injection and *t*earing"
15) Occipital Neuralgia: recurrent unilateral shooting pain lasting seconds over occipital region

DIAGNOSTICS

- R/O meningitis/encephalitis: HCT → LP (determine etiology), broad tx
- R/O SAH: HCT. If neg, MUST do LP (HCT less likely to see blood after 6 hours)
- R/O Pseudotumor: HCT. LP (check OP > 25 in decubitus position, legs extended *after tap* better)
- R/O dissection: CTA h/n acutely vs. MRI/A neck w/ T1 fat sats, add MRI brain to r/o accomp infarction

- R/O temporal arteritis: TA bruit/tenderness/pulselessness with elevated ESR. Consult vascular surgery for temporal artery biopsy.
- R/O hypertensive encephalopathy: watch BP, if focal or AMS. MRI to eval for PRES
- R/O VST: CTV vs MRV ("empty delta sign")
- R/O optic neuritis/myopathy: HCT, then MRI brain/orbits c/s gad, CK, admit for IV steroids for ON
- R/O acute migraine tension-type continuum: consider HCT if new HA syndrome

TREATMENT AND WORK-UP OF ACUTE MIGRAINE IN THE ED:
Remember the ED migraine pathway on Dorsata!

1st line: IV fluids, IV Reglan 10mg, and IV Toradol 15-30mg given at the SAME time
- if allergic to reglan, try procholorperazine, if allergic to Toradol can give PO tylenol
NOTE: If they don't have contraindications to a triptan can trial that here if early.

2nd line: Repeat 1st line medications 4 hours later. Can also add IV magnesium

3rd line: 250-1000mg IV solumedrol x 1 or Depakote IV load (15mg/kg, max 1g)
- If using depakote in young female must have negative pregnancy test
- try to avoid steroids in patients with brittle diabetes
- if steroids break headache consider steroid taper x 5-7 days to prevent rebound headache
- Ex. steroid taper: methylprednisolone 24, 20, 16, 12, 8, 4mg daily taper
- if Depakote breaks headache consider 500mg BID x 5 days to prevent rebound HA

Prevention: If >2 migraines/week, consider starting prophylaxis (riboflavin 400mg daily, magnesium oxide 400mg daily, nortriptyline 10-20mg qhs, topamax 25mg qhs) and schedule a follow-up with Neurology. See migraine management above for more details.

Workup: If any red-flag symptoms (focal deficit, atypical features of HA, new onset > 50, cancer/HIV, infectious symptoms, change in severity or quality), order MRI brain; most patients do not require imaging

PREGNANT HEADACHE

PRIMARY HEADACHES
- Migraine Headache: in general, retrospective studies have suggested that migraine frequency and severity decrease during pregnancy, particularly during the 2nd and 3rd trimesters. A prospective study of 49 patients showed 79% had complete remission of headaches by the third trimester. By one month postpartum, 50% had recurrence of migraine.
- Tension Headache: no change in frequency during pregnancy, but few data exist

SECONDARY HEADACHES
- Pseudotumor cerebri: see neuro-ophtho section
- Pre-eclampsia: new hypertension >140/90, proteinuria >300mg/dL; headache may precede development of serious neurologic sequelae (i.e. eclampsia with seizures)
- Subarachnoid hemorrhage: incidence may be higher in pregnancy (between 0.9-5/10,000) and during the six weeks postpartum, risk of SAH increases 28-fold
- Cerebral Venous Sinus Thrombosis: occurs in 1/2500-10,000 deliveries; especially likely if associated hypercoagulable states (protein C/S or antithrombin III deficiency, antiphospholipid antibody syndrome). Usually occurs in 3rd trimester but can occur up to 2-8 weeks postpartum.
- Postdural Puncture/Nonpostdural puncture: can occur with epidural & spinal anesthesia (CSF leak, pneumocephalus; other complications-subdural hematoma, aseptic/septic meningitis)

DIAGNOSTICS
1) Worrisome features: new-onset headache, change in pattern, visual changes, speech abnormalities, focal neuro signs/sxs, meningeal signs, trauma, seizure, history of malignancy
2) Detailed headache history & neurologic ROS; medications, diet

3) Vitals, neuro exam (including funduscopic exam to evaluate for papilledema)
4) Labs (urinalysis, pre-eclampsia labs)
5) Imaging: *if you suspect SAH* → non-contrast head CT (sensitivity ~90% in first 24 h of onset); it takes 50-100 head CTs to reach a concerning level of radiation exposure (5 rads!)
if you suspect VST → MRI/MRV without gad (although, if necessary, a CT venogram can be done). The National Radiological Protection Board advises against MRI in the first trimester, but there is no evidence to support the advisory.
6) LP: if imaging reveals no hemorrhage and the suspicion remains high, lumbar puncture is the only way to exclude SAH. Also indicated if suspicious of meningitis/encephalitis.

What's safe? See chart in migraine section

MOVEMENT

Special thank you to Dr. Aaron Lasker for their assistance in editing this section for the 2023-2024 guide.

In addition to your time on Movement Disorders elective, you may encounter movement disorder patients on consult service or in residency clinic on Thursdays when we have a dedicated movement clinic within resident clinic.

APPROACH TO THE MOVEMENT DISORDERS PATIENT/EXAM

The key of the movement disorders exam is largely based on **observation and description of an abnormal movement.** By using a specific framework and terminology, you can then classify the movement into several broad categories, each of which contains a more limited differential diagnosis, which serves as your "localization."

Hypokinetic versus Hyperkinetic

- Hypokinetic = akinesia (lack of movement), hypokinetic (reduced amplitude of movements), bradykinesia (slowness of movement) – **too few, too small, too slow**
- Hyperkinetic = excessive, often repetitive, involuntary movements – **too much, too big, too fast**

IF Hyperkinetic, then:

Is the movement **Jerky** or **Not-Jerky?**

- **Jerky (i.e. Non-rhythmic)**
    - Myoclonus = rapid, jerky, shock like movements – much too fast to be voluntary muscle activity
    - Chorea = A jerky, non-stereotyped and relatively slow movement that can flow between body parts
    - Tics = Brief, jerky, rapid, stereotyped movements that can be voluntarily suppressed followed by a rebound increase after the suppression
- **Not-Jerky**
    - Dystonia = a sustained muscle contraction that produces abnormal postures or twisting that can be patterned and directional
    - Athetosis = a writhing movement of flexion, extension, pronation, and supination of the fingers and hands
    - Tremor = Rhythmic, oscillatory (moves around a central point), caused by alternating contraction of opposing muscle groups

Further breakdown for *tremors*

Is the tremor seen in Rest versus Action

- Rest = tremor occurs when body part is supported so that skeletal muscle activation is not needed
- Action = tremor occurs in setting of voluntary muscle activation and has several flavors
    - Kinetic tremor = tremor occurs during voluntary movement
        - -Simple kinetic – tremor is the same throughout the voluntary movement
        - -Intention tremor – tremor increases as the body part approaches target
        - -Task specific tremor – tremor occurs during specific movement – like writing
    - Postural = tremor arises while a body part is held in a specific position (i.e. arms outstretched)

What is the frequency and amplitude?

- Tremors can be described as oscillations per second – "Hertz" – low = less than 4, medium = 4-7, high = >7
- Amplitude = Is the degree of movement large (high amplitude) or small (low amplitude)?

Where is the tremor -- Focal versus Segmental versus Generalized?

- Focal = one region of body affected (one arm, just voice, just jaw)
- Segmental = two or more contiguous body parts affected (i.e. arm + head)
- Hemitremor = one side of body
- Generalized = upper and lower body

Using this language to describe an exam

"I observed a low amplitude, medium frequency tremor that was worse in the right hand versus the left, and occurred at rest. The patient also displayed slow movements and a decrement in amplitude with repetitive movements, along with a slow, stooped gait." -- *Describing tremor in a PD patient*

"*My patient had a large amplitude tremor of both arms that I noticed increase in severity as they reached out to touch my finger, and they were not accurately able to hit my finger. I also noted a tremor of the trunk when trying to sit upright and a nodding tremor of the head"* -- *Describing intention/postural tremor in a patient with cerebellar degeneration*

Phenomenology Definitions
Acute Akathisia: A hyperkinetic (sensorimotor) movement disorder characterized by restlessness and the irresistible urge to move. Excessive movements that are complex, semi-purposeful, stereotypic, and repetitive, suppressible and decrease with distraction.
Ataxia: abnormal, uncoordinated movement
Bradykinesia: slowed movement with decrement in amplitude/speed or progressive hesitations/halts with continued movements
Chorea: Random, rapid, purposeless jerking, flowing movements
Dyskinesias: Like chorea, abnormal random, rapid purposeless movements usually related to Parkinson's levadopa therapy
Dystonia: Sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures. Often involves ocular muscles, head tilt backwards, tongue protrusion, forced jaw opening, arching of trunk, ocular deviation (limbs less often involved). Earliest abnormal involuntary movement to appear after initiation of dopamine receptor antagonist therapy.
Myoclonus: sudden, brief, shock-like movements; can be positive: muscle contractions or negative: loss of tone, asterixis
Parkinsonism: Refers to symptoms, not Parkinson's Disease: rest tremor, often asymmetric, cogwheel rigidity, bradykinesia, postural instability
Rigidity: velocity-independent resistance to passive movements

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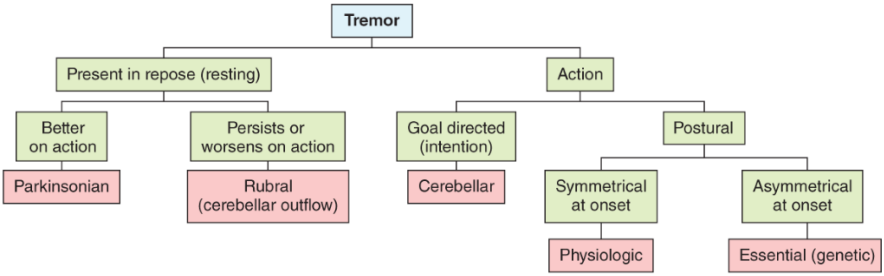
Tics: brief, intermittent motor or vocal tics; supressible for a period of time but then can be involuntary
Tremor: Rhythmic, oscillatory movements due to reciprocal contractions of agonist-antagonist muscles; further differentiation between rest tremor, postural tremor (with isotonic contractions), or kinetic tremor (with movement)



Branch Diagram for the tremor patient. From "Principles of Neurology" page 93.

TABLE 3-1 Differential Diagnosis of Unilateral Arm Tremor

Condition	Clinical Features
Parkinson's disease	Rest tremor; slow (4–6 Hz); associated with bradykinesia; rigidity (lead-pipe or cogwheeling). Re-emergent on holding out arms. Present when walking. Can also have unilateral leg tremor. Face and jaw tremors may occur.
Dystonic tremor	Rest and postural tremor; slow frequency. Associated with involuntary postures due to dystonia in fingers and arm; possible bradykinesia; possible rigidity. Dystonia may be present in other body parts.
Essential tremor	Postural and intention tremor; high frequency; more commonly bilateral tremor but can be asymmetrical; tremor may be present in neck, voice, legs.
Holmes tremor	Rest, postural, and intention tremor; worsens from rest to intention; low frequency; often associated with ataxia and dystonia.

From Walsh et al. "What Do I Do Now? Movement Disorders" 2017, page 18.

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PARKINSON'S DISEASE

Overview*:* A progressive neurodegenerative (alpha synucleopathy) disease characterized by an **asymmetric resting tremor**, **rigidity**, **brady/Akinesia**, and **postural instability (late in disease course) AKA TRAP…**The disease is not limited to motor symptoms and you must watch out for an array of neuropsychiatric manifestations that can significantly impair quality of life. Typical age of onset is 55 years and older, 90% are sporadic

Diagnosis*:* We will all have patients referred to resident clinic who have been told they might have PD. While classic PD can be hard to mistake, there are a number of conditions that can overlap with PD so a careful evaluation is needed before making a PD diagnosis.

Based on Movement Disorder Society Criteria on exam you **need** to have motor parkinsonism – **Bradykinesia** and **Rest Tremor** or **Rigidity.**

-You can support your diagnosis with:

- **Clear response to treatment with dopaminergic drugs**. A dramatic response, where the patient returns to basically a normal level of functioning is very suggestive. Improvement with Levodopa dose increases/worsening with decreases, along with on/off fluctuations is also supportive.
- + Levodopa dyskinesias
- **Rest tremor in limb**

-Then you need to **rule out absolute exclusion criteria** (not all included here)

- Are there cerebellar signs (ataxia, sustained gaze evoked nystagmus, ataxic gait)? If yes, reconsider diagnosis (see "the ataxic patient" below)!
- Can they not look down? If yes, reconsider diagnosis (see "atypical parkinsonism" below)!
- Were they being treated with a dopamine deplete/blocker when symptoms began? If yes, reconsider diagnosis!
- Does their tremor/bradykinesia/rigidity not get the least bit better despite high doses (>1000 mg daily) of Levodopa? If yes, reconsider diagnosis!
- Do they have obvious limb ideomotor apraxia/progressive aphasia/behavioral variant FTD? If yes, reconsider diagnosis (see Cognitive Section)!

-Look for **softer "red flags"** that should call into doubt the diagnosis of PD

- Rapid progression of gait impairment – patient in wheelchair 5 years after symptom onset
- No motor symptoms after five years
- Early bulbar dysfunction – severe dysphonia/dysarthria/dysphagia
- Severe autonomic failure in first five years (see atypical parkinsonism section – MSA) – orthostatic hypotension, urinary retention/incontinence
- Recurrent falls 2/2 imbalance within first three years of onset
- Unexplained weakness or very significant hyper-reflexia
- Totally symmetric parkinsonism

Is neuroimaging helpful in diagnosing PD?

Generally, neuroimaging is not useful in a patient who presents with classic PD, but there are several instances where you may want to get a scan:

1) Presence of particular red flags – significant hyperreflexia/weakness, cerebellar signs, significant autonomic instability, vertical opthalmoparesis – an MRI can help look for signs of cerebellar degeneration, or brainstem findings suggestive of MSA/PSP

2) The patient was diagnosed with Essential Tremor a long time ago, but has come to see you and you think their tremor looks a good deal Parkinsonian – consider a **DaTscan – striatal dopamine transporter imaging -- (but make sure they aren't taking amphetamines, cocaine, bupropion)**

3) patients with neuroleptic exposure with progressive movement symptoms on stable medication doses.

<u>If you are considering a DAT scan it makes sense just to send them to movement clinic.</u>

PARKINSONIAN SYNDROMES

Idiopathic Parkinson's Disease	Multiple system atrophy[1]	Progressive supranuclear palsy[2]	Corticobasal degeneration[3]	Dementia with Lewy bodies[4]
Unilateral onset of symptoms Presence of slowness of repetitive finger taps with fatigueable decrement Presence of a resting tremor Presence of unilateral reduced arm swing Postural instability but usually no falls at diagnosis and early disease Good response to levodopa treatment	Symmetrical symptoms, rapid progression Early falls, often backwards Disproportionate antecolles Camptocormia Autonomic dysfunction Stridor Snoring Involuntary sighing Emotionally labile	Reduced eye movements, especially downwards Early falls, often backwards Motor recklessness 'Mona Lisa' stare Positive applause sign Cognitive changes Behavioural changes Emotional lability	Reduced coordination/function in one upper limb Cognitive dysfunction Pout reflex Pallilalia Echolalia	Hallucinations at diagnosis Fluctuating cognitive changes Impairment in attention, executive and visuo-perceptual function Parkinsonian features e.g. tremor, rigidity bradykinesia, shuffling gait which respond less well to levodopa treatment

From Lindop et al. "Atypical Parkinsonism: Making the case for a neuropalliative rehabilitation approach" IJTR 2014.

Treating the Patient:

<u>Treatment of motor symptoms</u> in PD is typically initiated when symptoms lead to an interference with function.

None of the therapies presented in the table below are proven to slow down disease progression, they only treat symptoms.

Initial choice of medication is **between Carbidopa/Levodopa** and several other antiparkinsonian drugs – **dopamine agonists (main levodopa alternative), monoamine oxidase B (MAO-B) inhibitors, amantadine, or anticholinergic**.

- Biggest concern with Levodopa is the development of motor fluctuations and dyskinesias – present in at least 50 percent of patients after 5-10 years of therapy; risk increases with younger age of PD onset.
- Biggest concern with dopamine agonists includes impulse control disorders.

With early PD and very mild symptoms you can consider using a MAO-B inhibitor or amantadine.

Younger patients (<65) with more significant symptoms can be started on Levodopa or a dopamine agonist after discussion of risks/benefits, although symptomatic control is better with Levodopa.

Older patients (>65) with more significant symptoms are better served with Levodopa due to poor tolerability of the dopamine agonists.

Refer to PT/OT/SLP at Pennsy – order can specify LSVT BIG (PT/OT) + LSVT LOUD (Speech therapy)

<u>NOTE: Do not stop PD meds abruptly! Before discontinuing always check Lexicomp/UpToDate/Discuss with an attending for guidance</u>

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PD medications

DRUG	MECH.	USE	DOSING	SIDE EFFECTS
Carbidopa/Levodopa (Sinemet) Comes as orally disintegrating tablet (Parcopa) Comes as CR formulation (used at bedtime for nocturnal PD symptoms) Comes as ER capsule (Rytary) Comes as inhaler (Inbrija) Comes as intestinal infusion via J tube (Duopa)	Levodopa is a DA precursor; Carbidopa is a dopa decarboxylase inhibitor	Motor symptoms	Start 25/100 mg 0.5 tab bid-tid (qd for elderly or cog impairment); Titrate up by 0.5 tab/day every 3-7 days (slower if elderly or cog impairment); Typical doses 300-600 mg/day divided tid at meal-time; May be increased or given more frequently as disease progresses	Nausea (can take with food) Sedation Lightheadedness/orthostasis Confusion Hallucinations/delusions Dyskinesias Impulse control disorder (less likely than with DA agonists)
Entacapone (Comtan), Tolcapone Comes as a combination tab with carbidopa/levodopa (Stalevo)	COMT inhibitor	Motor symptoms, (wearing off)	200 mg tablet given with dose of carbidopa/levodopa (max 8 doses/day)	Enhanced dopaminergic effects (e.g., sedation, nausea, confusion/psychosis, orthostasis, dyskinesias) GI upset, diarrhea, hepatotoxicity Orange discoloration of urine
Pramipexole (Mirapex) Comes as Mirapex ER (once daily dosing)	DA agonist	Motor symptoms	0.125 mg tid x 1 week, 0.25 mg tid x 1 week, 0.5 mg tid Maintenance doses usually 1.5-3 mg/day Max 4.5 mg/day	Nausea, sedation (sleep attacks), orthostatic hypotension, confusion, psychosis, dyskinesias, peripheral edema, impulse control disorder
Ropinirole (Requip) Comes as Requip XL (once daily dosing)	DA agonist	Motor symptoms	0.25 mg tid, increase 0.25 mg/dose weekly for 4 weeks to total daily dose of 3 mg, then increase by 1.5 mg/day each week up to 9 mg/day and then by 3 mg/day each week up to max 24 mg/day. Maintenance doses typically 12-16 mg/day	Same as Pramipexole
Carbidopa (Lodosyn)	dopa decarboxyl-ase inhibitor	Nausea related to Sinemet	12.5-25 mg with doses of Sinemet	Enhanced dopaminergic effects

Selegiline (Eldepryl)	MAO-B inhibitor (Nonselective MAO-A/ B at higher doses)	Motor symptoms (mild benefit), wearing off, ?neuro-protective	Start 5 mg in the morning, can increase to 5 mg bid after 1 week Second dose given midday/early afternoon to avoid insomnia (doses > 10 mg/day likely not effective)	Enhanced dopaminergic effects Insomnia (amphetamine met) Hypertensive crisis (doses >10 mg/day associated with MAO-A inhibition and dietary interactions with tyramine-containing foods) Drug interactions (monitor for risk of serotonin syndrome with TCAs, SSRIs)
Rasagiline (Azilect)	Selective MAO-B inhibitor	Motor symptoms (mild benefit), wearing off, ?neuro-protective	1 mg daily	Enhanced dopaminergic effects Drug interactions Less likely to cause hypertensive crisis
Amantadine (Symmetrel)	Uncertain-DA stimulation, anti-cholinergic, NMDA receptor antagonism	Motor symptoms (mild/transient benefit, can be helpful for tremor); motor fluctuation dyskinesia	Start 100 mg daily, increase by 100 mg a day each week to 100 mg tid 100 mg bid often effective No benefit >300 mg/day	Enhanced dopaminergic effects Edema Livedo reticularis Sleep disturbance (nightmares, insomnia)
Trihexylphenidyl (Artane)	Anti-cholinergic	Motor symptoms, tremor Usually poorly tolerated in elderly	Start 0.5-1 mg qd-bid and increase gradually to 2 mg tid	Sedation, cognitive impairment, confusion, psychosis, nausea dry mouth, urinary retention, constipation, blurred vision, tachycardia, impaired sweating, acute closed-angle glaucoma

Non-motor symptom management

1) Depression

- Very common, as is suicidal ideation and thoughts of death
- Few studies have been performed, but limited data suggests that SSRIs/SNRIs so not worsen motor function. **Be aware for serotonin syndrome with drugs like MAOB inhibitors!**
- If SSRIs ineffective can trial TCA, but must be very careful about anticholingergic side effects à cog impairment and orthostatic hypotension + falls

2) Psychosis

- Paranoid delusions + visual hallucinations (up to 40% of patients)
- Can be triggered by meds (like dopamine agonists), dementia, delirium, infection
- Treat if psychosis impairs function
  -If **meds** are thought to be culprit can **wean/discontinue** in following order (balance risk of worsening motor symptoms): Anticholinergics, amantadine, dopamine agonists, MAO-B inhibitors, COMT inhibitors, Levodopa

-Can trial a **cholinesterase inhibitor** (i.e. Rivastigmine patch), although effect in studies is mild and effect can be temporary

-Atypical antipsychotics **Prescribe cautiously, associated with increased mortality**

Quetiapine: Start at 12.5 mg at night, can titrate up to 100 mg at night

Pimavanserin: Newer agent (app. 2016), 2nd gen antipsychotic drug that acts as a selective serotonin 5-HT2A receptor inverse agonist – dosed as 34 mg once daily

Clozapine: Initial: 6.25 mg/day, in 1 or 2 divided doses; increase daily dose based on response and tolerability in 6.25 or 12.5 mg increments at intervals of 3 to 7 days to a maximum dose of 50 mg/day. There is a patient registry that patients must be added to so you will need to do this in cooperation with one of the movement disorder attendings.

3) Excessive daytime sleepiness/Fatigue

- Try to make contributing med changes if possible – i.e. reduce dopamine agonist
- Pharmacological therapies

  -Judicious daytime caffeine use – slight improvement in somnolence in RRCT with 121 patients, but slight increase in dyskinesias

  -Modafinil and methylphenidate – used when nothing else works, but data is mixed and benefit is mild and usually not sustained

4) Orthostatic hypotension

- May occur as feature of disease or side effect from PD meds
- Nonpharmacologic treatment

  -Bolus water intake (most effective therapy), high salt diet, abdominal bands, compression stockings
- Pharmacological therapies

  -Midodrine, fludricort, droxidopa likely referring to PCP/Cardiologist to start/titrate these therapies

Additional resources for PD patients

Pennsy Movement Disorders Center has a number of resources for PD patients – information materials (sleep, mood, psychosis) and small groups

You can steal Michael Baer's .ptinforparkinsonscenter dot phrase which provides URL's for patients/caregivers so they can access the above

Random information you may need

1) *Troubleshooting non-formulary PD meds*

- If possible, especially with the new extended release formulation (rytary), have patient bring in their meds, get approved by the pharmacy, and have them take their own meds.
- If they can't bring in their own meds, look at the levodopa dosage of what they are taking, and convert to a roughly equivalent dose of carbidopa-levodopa (sinemet, on formulary).
- Parcopa is identical to Sinemet except that it dissolves orally (it is still absorbed in the intestine, not orally).
- If they take Stalevo, keep the interval between doses the same as what they take at home.
- If entacapone is on formulary, order it separately (always 200 mg) and at the same times as their Sinemet doses; if it's not, just do without it.
- *Make sure you don't just order "q8h" if they take a med TID; see what times they take it at home!*
- For Rytary, ask the patient (or look in EPIC if they're seen here) and give them what they were taking of sinemet before they switched to Rytary

2) Patient is NPO

- Place Dobhoff and give meds this way. If pt has SBO see if surgery is willing to still give meds and clamp tube for 15 min after. There is no IV formulation of any PD drugs. There is the neupro patch (dopamine agonist) but if the patient is not used to this drug it can cause lots of side effects (hypotension, confusion, hallucinations), and it is probably not on formulary anyway; would defer on this until consulting with the pt's neurologist.
    - For giving meds via NGT: If they are controlled-release convert dosing to immediate release. Controlled release dopamine agonists (Requip XL, Mirapex ER) can be converted to their immediate-release equivalents by dividing total XL/ER dose by 3 and giving q8 hours. If they are on controlled-release sinemet, use same dose and interval for the immediate release to start, and adjust as needed.

3) DBS FAQs (may get phone calls/curbsides with these questions)

- *Is my DBS on?*

You will need the patient programmer to check this. The power button for the patient programmer is the small grey button at the bottom of the programmer. Hold the programmer up to the DBS IPG (implantable pulse generator) in the patient's chest, and press the orange check-mark button. If you hear three beeps and/or there is a question mark on the screen, the remote did not find the device - relocate and try it again. If you hear a solid beep the screen will most likely say "On", "Ok", and have one or two numbers on the bottom. If the stimulator is off, it will be blinking "Off" instead of saying "On". If the battery needs replacement, instead of saying "Ok", it will read "ERI" (elective replacement indicator) or "EOS" (end of service). If you see this, neurosurgery should be called in the morning to schedule replacement.

- *How do I turn the DBS on or off?*

After syncing the device as above (with the orange check-mark button), press the large grey button next to the large orange button. This will turn the stimulator on or off.

- *When should the stimulator be off?*

During EKGs, during MRIs, during any surgery or procedure in which electrocautery will be used.

- *What kind of MRI can be done with DBS?*

Only a **brain** MRI with a receive-only head coil. Even with this head coil the DBS MUST be turned off. Most facilities only have transmit-receive head coils and can't do this. PAH has a receive-only head coil. Patients with DBS CANNOT get an MRI of ANY other body part.

- *For what symptoms should I click up or down?*

Clicking up the voltage will usually help Parkinson's symptoms, such as tremor, stiffness, slowness, and walking. If the patient is having side effects from stimulation, such as speech effects, facial pulling or contractions, or tingling, clicking down the voltage will usually help.

- *What are groups/what do the letters mean?*

Some patients will have several settings that they can switch between, rather than just being able to click their voltage up or down. These different settings are called groups, and have a letter from A-D. If we create new settings at a visit, we will usually create a new group (ie,

group B) to do this, and then if they don't like the setting, they can switch back to the old setting (ie, group A) at home with their patient programmer.

- *What about the other parameters that can be adjusted?*

We can also adjust pulse width and frequency, but we don't usually give patients the ability to adjust these. Patients generally only have the ability to adjust voltage.

DEMENTIA WITH LEWY BODIES (DLB)/PARKINSON DISEASE WITH DEMENTIA (PDD)

Overview: Degenerative disease marked by Lewy bodies strewn throughout neocortex, brainstem, and limbic structures…DLB (Dementia before PD) and PDD (dementia w/ well established PD) distinguished by temporal sequence of clinical characteristics but distinction is arbitrary. Common cause of dementia (behind AD/vascular dementia). Average age of presentation is 75 with a male predominance. Early motor symptoms and psychiatric symptoms can lead to early institutionalization.

Making the Diagnosis*:*

1) First there must be dementia – usually see deficits in attention, executive function, and visuospatial ability
2) Second, look for core clinical features including:
   - **Fluctuating cognition** w/ variations in alertness/attention (60-80%)
   - Recurrent **visual hallucinations** that are well formed (70%)
   - **REM sleep behavior disorder** (85%)
   - **Parkinsonism** (70-90%)
3) Diagnosis supported by:
   - Antipsychotic sensitivity – parkinsonism, impaired consciousness, features of NMS
   - Repeated falls
   - Excessive day time sleepiness
   - Delusions

Differential diagnosis:

PDD – if there is parkinsonism for 1 year prior to dementia onset then the official classification is PDD. There is debate about whether this is an arbitrary distinction

AD – delirium on top of AD can mimic the fluctuations seen in DLB, or extrapyramidal side effects from meds can cause parkinsonism in AD patients

Treating the Patient*:*

1) Cognition and Neuropsych symptoms

- Cholinesterase inhibitors are first line – used to treat cognition, fluctuations, and psychosis
  -Rivastigmine -- Oral (1.5 mg BID, can increase by 3 mg daily every 2 weeks to 6 mg BID) or Patch (4.6 mg/24 hours patch daily. After 4 weeks can increase to 9.5 mg/24 hours daily. Max dose is 13.3 mg/24 hours daily
  -Donepezil -- 5 mg daily, can increase to 10 mg daily after 4 weeks. Then can go to 23 mg daily after another 3 months
  -Side effects -- Nausea, vomiting, diarrhea, urinary frequency, weight loss, case reports of worsening REM sleep behavior disorder, parkinsonism

- Atypical antipsychotics
  -Only use these as a last resort if psychosis is posing a danger to the patient
  -Only use atypical antipsychotics, and do not titrate up significantly -- would discontinue and try alternative agent instead

2) REM sleep behavior disorder (see Sleep Medicine section)

- Ensure safe sleeping environment
- Start with Melatonin – 3 to 15 mg at night – fewer side effects – improvement generally seen above 6 mg at night
- Next agent to try is Clonazepam – 0.25 to 1.5 mg at night – does have added benefit of treating anxiety

3) Parkinsonism

- Similar to PD, but usually with less success
- Levodopa has fewer side effects, should start low and titrate up slowly to avoid worsening psychiatric symptoms – start at ½ tab 25/100 Sinemet and TID and titrate up slowly over several weeks
- Avoid anticholinergics due to risk of worsening cognition

ATYPICAL PARKINONISM – AKA PARKINSON'S PLUS SYNDROMES

PROGRESSIVE SUPRANUCLEAR PALSY

Overview: Progressive tauopathy that leads to postural instability, falls (backwards), supranuclear palsy (slowed vertical saccades several years into disease), and bulbar symptoms…can also see bradykinesia with axial rigidity and frontal lobe impairment.

NOTE: there are a ton of clinical subtypes! PSP with predominant Parkinsonism, PSP with oculomotor dysfunction, PSP with progressive gait freezing…

Making the Diagnosis: occurs in patients > 40 with four clinical domains impacted, with some features given high weight than others when deciding on a diagnostic certainty (as denoted by the >):

- Oculomotor dysfunction – vertical supranuclear gaze palsy > slow velocity vertical saccades > square wave jerks or eyelid opening apraxia
- Postural instability – repeated unprovoked falls > tendency to fall on pull test > more than two steps backwards on a pull test
- Akinesia – progressive gait freezing > levodopa resistant parkinsonism
- Cognitive dysfunction – progressive nonfluent agrammatic aphasia or speech apraxia > frontal cognitive changes > corticobasal syndrome

Useful tests

- An MRI brain will show midbrain atrophy with a preserved pons – the "hummingbird sign" on sagittal imaging or "Mickey Mouse" on axial imaging
- Levodopa response to differentiate with PD
- Given progressive nature of the disease, be sure to rule out treatable mimics – Wilson's, hypothyroidism, neurosyphilis, Whipples, paraneoplastic syndromes

Treating the patient:

- Unfortunately not curable – consider early palliative care involvement
- Involve PT/OT/COPE early – can link in with the **COPE clinic at PAH – where patients can see multidisciplinary team multiple times per year**
- Levodopa may provide a transient benefit to some patients with parkinsonism
- Botox for focal dystonia

MULTIPLE SYSTEMS ATROPHY

Overview: Progressive alpha synucleinopathy with a variety of phenotypes. Mean age of onset is 54. Male predominance. Generally sporadic. Wheelchair in 3-5 years, death in 6-10. Will see combo of akinetic-rigid parkinsonism, autonomic failure, cerebellar ataxia, and pyramidal signs. Two subtypes based on type of motor impairment

- MSA with predominant parkinsonism (MSA-P) – akinesia/bradykinesia, rigidity, postural instability, irregular jerky postural/action tremor, falls, camptocormia (bent spine syndrome), anterocollis, hemiballism, chorea, stimulus sensitive myoclonus
- MSA with predominant cerebellar ataxia (MSA-C) – gait/limb ataxia, dysarthria, gaze-evoked nystagmus, impaired smooth pursuits, ocular dysmetria

Making the diagnosis: A sporadic, progressive, adult-onset disease characterized by autonomic failure (urinary incontinence or orthostatic hypotension) **and** poorly levodopa responsive parkinsonism) **or** a cerebellar syndrome.

Useful tests

- MRI brain will show putamen, middle cerebellar peduncle, and pontine atrophy/hyperintensity. "Hot cross bun sign" with olivopontocerebellar and middle cerebellar peduncle atrophy.
- Failed levodopa response -- may need to titrate up to high doses to be sure
- You may need to do genetic testing to differentiate MSA from an SCA, fragile X ataxia syndrome

Treating the patient

- See PSP section – refer to COPE clinic at PAH
- Botox for focal dystonia
- Be on the lookout for sleep issues – sleep study/CPAP
- Manage orthostasis with fludrocortisone (first choice), midodrine/droxidopa (second choices)
- Oxybutynin for detrusor hyperreflexia
- Screen for depression
- The MSA Coalition for support groups

CORTICOBASAL SYNDROME (CBS)

Overview: Rare disorder that p/w asymmetric mix of cognitive deficits, akinesia, rigidity, dystonia, ideomotor apraxia, alien limb phenomenon. Pathologically very mixed . CBS refers to a clinical diagnosis. Corticobasal degeneration (CBD) refers to a pathological diagnosis of a specific type of tauopathy. Pathologically see variable involvement of frontal/parietal/temporal lobes contralateral to the affected side. May initially present to cognitive clinic or movement d/o specialist depending on presentation.

Making the diagnosis: Consider diagnosis in patient w/ unilateral limb apraxia, limb rigidity, alien limb phenomena (involuntary motor activity of limb with feeling of estrangement from limb), deficits in language function (reduced word fluency) and visuospatial dysfunction.

- Patients may appear similar to PD patients (hence referrals to movement specialists). Patients with underlying CBD will not respond to Levodopa like PD patients.

Useful tests

- Not a great way to differentiate from other diseases based on structural imaging/PET imaging. Essentially remains a clinical diagnosis.

Treating the patient:

- Poor response to typical PD medications
- Can consider botox for dystonic spams is present
- Screen and treat depression
- PT/OT early on, make sure gait is safe

WILSON'S DISEASE

MOVEMENT

Overview: AR disease (ATP7B mutations) of impaired cellular copper transport…affects liver, brain, cornea (K-F rings). Starts in 20s—30s. 50% present with neuropsych signs of tremor, ataxia, dystonia, psychosis, parkinsonism, chorea, dysarthria

Making the diagnosis: If you suspect the diagnosis based on the above, send serum ceruloplasmin + slit lamp exam for Kayser-Fleischer rings. If both are present/high then jump straight to molecular genetics. If the first two are conflicting you may need a 24-hour urine copper (should be high in Wilson's)

Treating the patient:

- Remove copper from body with chelator D-penicillamine. This is poorly tolerated and may need to switch to Trientine and has less side effects.
- Can use oral zinc salts to prevent copper absorption in the gut
- Low copper diet – can't eat liver unfortunately

ESSENTIAL TREMOR

Overview: Bilateral, slightly asymmetric, upper extremity action and postural tremor of high frequency, low amplitude. Less commonly affects the head/voice/trunk. Very slowly progressive. Positive family history in 30-70%. Improves with EtOH.

Making the Diagnosis: Look for **isolated bilateral upper limb action** (kinetic and postural) tremor without motor abnormalities. 3+ years duration. Absence of other neurological signs like dystonia, ataxia, parkinsonism

- NOTE that an **isolated head tremor does not meet criteria for ET**! In this setting it is important to rule out cervical dystonia.
- Rule out mimics like PD, enhanced physiological tremor, and cervical dystonia
- Generally imaging is not needed unless there are atypical features. For instance, if you are debating between ET and PD a DaT Scan could be useful.

Treating the Patient:

- **Propanolol** – start at 40 mg BID and titrate up to 120-320 mg per day based on symptoms and bradycardia
  - *Avoid use in asthma, heart block, diabetes
  - *NOTE: **you can use propanol PRN for mild ET** with situational worsening of tremor
- **Primidone** – start at 25 mg QHS – increase 25 mg every 3 days up to 400 mg QHS. Look out for sedation, nausea/vomiting, and vertigo
- **Less frequently used** – gabapentin and topiramate

Refractory ET – botox, DBS, focused ultrasound

Difficulty with ADLs? You can refer to OT at PAH, there are adaptive devices out there that can improve functioning, like weighted stabilizing spoons

DYSTONIA

Overview: Sustained or intermittent muscle contractions causing abnormal movements/postures…movements are typically patterned and twisting. Will often resemble a tremor. Cervical dystonia is most common. Can be sustained or task specific (like writer's dystonia). Many patients have a "sensory trick," a maneuver that helps symptoms abate

Making the diagnosis:

Dystonia can be broken into different classifications

- Age of onset: infancy, childhood (3-12), adolescence (13-20), early adulthood (21-40), late adult (>40)
- Body distribution: focal (single body region), segmental (2+ contiguous regions), multifocal (2+ non contiguous body regions), generalized (trunk + 2 sites), hemidystonia (restricted to one side)

- Temporal pattern: static vs progressive; variability: persistent, action-specific, diurnal, or paroxysmal
- Associated features other than tremor: myoclonus, parkinsonism, etc

Dystonic syndromes

- Early onset: may start focal then generalized – familial AD – DYT-TORIA, DYT-THAP1, dopa-responsive dystonia (Segawa disease)
- Adult onset focal: usually in upper body, >30 years

1) Cervical dystonia: head turning, neck extension
2) Blepharospasm: blinking, spasms, involuntary eye closure
3) Oromandibular dystonia: jaw clenching, jaw opening, tongue protrusion
4) Spasmodic dysphonia: vocal cord/laryngeal muscle dystonia causing speech breaks +/- vocal tremor
5) Task specific: writer's, golfer's, musician's, typist's

- Combined dystonia: dystonia-parkinsonism, myoclonus dystonia, paroxysmal dyskinesia with dystonia
- Acquired dystonia: perinatal birth injury, cerebrovascular, brain injury, medications (AEDs, Ca channel blockers, dopamine agonists, dopamine receptor blockage – antipsychotics, metoclopramide, levodopa), infection (HIV, SSP, syphilis, TB, viral encephalitis), brain tumor, paraneoplastic/autoimmune encephalitis, toxicity (3-nitroproprionic acid, carbon disulfide, cobalt, cyanide, disulfram, manganese, methanol)

Workup:

- Levodopa trial to confirm/exclude dopamine-responsive dystonia if FH, young onset, or h/o PD
- Genetic testing: If early onset, FH, or suspicion for genetic syndrome
- CT/MRI: can assess for structural lesion
- Labs: CBC, BMP, LFTs, ANA, ceruloplasmin/copper, ESR, RPR

Treating the patient:

- Levodopa if dopamine responsive
- Anticholinergics: trihexyphenidyl – start 1 mg BID and uptitrate 2 mg/week to 15 mg/day
- Benzos, VMAT2 inhibitors (tetrabenazine), baclofen can also be helpful
- Botox: For focal dystonias (i.e. cervical dystonia)
- DBS

CHOREA

Random, rapid, purposeless jerking, flowing movements

DDx: mostly acquired vs genetic.

1) Start a workup for acquired thinking of the list below (See Aaron Lasker's dotphrase: ALCHOREADDX) or https://www.movementdisorders.org/MDS-Files1/News/Archived-Content/choreaposter12.pdf
2) Refer to Huntington's clinic for consideration of genetic testing if the acquired workup is negative.

DDx for acquired chorea:

Paraneoplastic (anti Hu, Yo, CRMP5, IgLon5, Caspr2), acquired hepatocerebral degeneration, anti phospholipid antibody syndrome, Lupus, HIV, Celiac disease, polycythemia vera, Wilson's disease (hepatolenticular degeneration), CJD, metal deposition diseases (NBIA, neuroferritinopathy),

chorea gravidarum, tardive dyskinesia, hyperthyroid chorea, vascular hemichorea (including carotid stenosis), Sydenhams' (post-infecious) chorea.

THE ATAXIC PATIENT

Cerebellar anatomy overview

- *Midline cerebellar structures* – cerebellar vermis, fastigial and interposed nuclei, vestibulocerebellum, paravermis/intermediate zone – deficits lead to truncal ataxia, dysmetria (legs), saccadic intrusions, horizontal gaze evoked nystagmus, ocular dysmetria (overshooting target)
- *Cerebellar hemispheres* – damage leads to dyskiadochokinesis (incoordination with rapid alternating movements), dysmetria of hands/arms, limb ataxia, intention tremor, scanning speech

Approach to the patient – *acute (seconds to days), subacute (days to weeks), chronic (months to years)*
1) Acute – Stroke/hemorrhage, meds (sodium channel blockers, benzos, phenobarb), chemo (cytarabine, fluorouracil), EtOH, infection (meningoencephalitis or postinfectious cerebellitis)
2) Subacute – PML, Prion disease, Whipple disease, ADEM, celiac disease (gluten enteropathy with ataxia), Miller Fisher syndrome/Bickerstaff encephalitis, anti-GAD, anti-Yo, Anti-Hu, anti-Ri, Anti-Ma, primary tumors/mets, heavy alcohol use (cerebellar vermis) and Wernicke's
3) Chronic + progressive – genetic conditions account for 1/3-1/2 in adults

- Autosomal dominant
  -Spinocerebellar ataxias – genetically/clinically heterogeneous – SCA1-SCA 48 currently…many SCAs have features beyond cerebellar ataxia…several caused by CAG repeat expansions
  -Dentatorubral-pallidoluysian atrophy (DRPLA) -- myoclonic epilepsy, dementia, ataxia, and choreoathetosis – seen mainly in Japan and North Carolina
  -Episodic ataxias – paroxysmal disorders starting in childhood with brief bouts of cerebellar dysfunction…seven subtypes…EA1 and EA2 are caused by channelopathies and can respond to acetazolamide

- Autosomal recessive
  -Friedreich ataxia – most common hereditary ataxia w/ progressive gait and limb ataxia…also see optic atrophy, UMN weakness, peripheral neuropathy…cardiomyopathy/DM also seen…GAA repeat expansion in FXN gene…death between 30-40 years
  -Hereditary vitamin E deficiency – mutation in alpha-tocopherol transfer protein or from abetalipoproteinemia (can't absorb the vitamin E/other fat soluble vitamins)…teens/early adulthood…supplement with vitamin E
  -And many more…

- X-linked
  -Fragile X associated (FXTAS) – older men who are carries of the premutation in the FMR1 gene consisting of a CGG repeat expansion from 55 to 200 repeats…very common mutation with incomplete penetrance depending on repeat length…progressive ataxia with prominent intention tremor around age 50…may see cog decline, parkinsonism, neuropathy, autonomic dysfuction…treatment is symptomatic

Laboratory tests to consider for the patient with cerebellar ataxia

Most patients should have:
Complete blood count with peripheral smear
Creatinine
Electrolytes including calcium and magnesium
Erythrocyte sedimentation rate
C-reactive protein
Liver function tests
Thyroid function tests
Vitamin B12, vitamin E, and serum copper levels (for vitamin deficiencies)
Serum ceruloplasmin and 24-hour urine copper (for Wilson disease)
Serum lactate and pyruvate (for mitochondrial disorders)
Consider in selected patients:
Lumbar puncture for CSF cell count, protein, glucose, cultures, oligoclonal bands, cytology, lactate, 14-3-3 protein, and cerebellar autoantibodies
Genetic testing (see text)
Serum thiamine*
Anti-glutamic acid decarboxylase (GAD) antibodies (for GAD antibody-associated ataxia)
Anti-gliadin, anti-tissue-transglutaminase and anti-endomysial antibodies (for celiac disease)
HIV, RPR, and Lyme disease testing
Alpha-fetoprotein (for AT, ATLD, and AOA type II)
Lipids (for AOA type I and abetalipoproteinemia)
ACE, ANA, Ro/SSA, La/SSB, C-ANCA, P-ANCA, and anticardiolipin antibodies (for systemic immune disorders)
Paraneoplastic antibodies
Cholestanol (for cerebrotendinous xanthomatosis)
Phytanic acid level (for Refsum disease)
Urinary heavy metals (for toxic causes)
Plasma amino acids, urine organic amino acids, and very long chain fatty acids (for various inherited metabolic disorders)
Serum ammonia level (for urea cycle disorders)

ACE: angiotensin converting enzyme; ANA: antinuclear antibody; ANCA: antineutrophil cytoplasmic antibodies; AOA: ataxia with oculomotor apraxia; AT: ataxia-telangiectasia; ATLD: ataxia-telangiectasia-like disorder; CSF: cerebrospinal fluid; HIV: human immunodeficiency virus; RPR: rapid plasma reagin (for syphilis).
* When Wernicke encephalopathy is suspected, immediate thiamine replacement takes precedence over laboratory diagnosis.

UpToDate®

From Todd et al. "Overview of cerebellar ataxia in adults." UpToDate.

ACUTE

CONDITION	DRUGS	MANAGEMENT
Acute drug-induced movement disorders		

MOVEMENT

Dystonia	DA-blocking antiemetics (e.g., metoclopramide, prochlorperazine), antipsychotics (e.g., olanzapine, risperidone, aripiprazole, haloperidol, pimozide, molindone, thioridazine, fluphenazine, chlorpromazine), cocaine, methamphetamine	Taper/eliminate drug if possible For acute dystonic reaction: Diphenhydramine 25-50 mg IV Benztropine 1-2 mg IV
Akathisia	DA-blocking antiemetics and antipsychotics, SSRIs, cocaine, methamphetamine, tetrabenazine	Taper/eliminate drug if possible Propranolol (start 10 mg, often requires <80 mg/day) Anticholinergics may worsen acute akathisia
Chorea	PD meds: Levodopa > dopamine agonists; worse with adjunctive meds such as COMT and MAO inhibitors Cocaine, methamphetamine, ETOH, oral contraceptives, anticonvulsants, TCAs/SSRIs, discontinuation of DA-blocking antiemetics or antipsychotics (withdrawal emergent syndrome)	Dyskinesias in PD: Decrease dose of levodopa and/or dopamine agonist as possible Consider stopping/reducing adjunctive medications Consider adding amantadine for levodopa-induced dyskinesias (start 100 mg daily; increase up to 100 mg tid) Clonazepam (start 0.25-0.5 mg, increase gradually) Withdrawal emergent syndrome: restart drug and slowly taper
Parkinsonism	DA-blocking antiemetics and antipsychotics; also methyldopa, reserpine, tetrabenazine, SSRIs, verapamil, dilantin, captopril, amiodarone, lovastatin, valproic acid, meperidine, amphotericin B, bethanechol, mestinon, tacrine, lithium, ara-C, MPTP, flunarizine, cinnarizine, manganese (in TPN)	Taper/eliminate drug if possible
Postural and kinetic tremor	nicotine, TCAs/SSRIs, lithium, EtOH, B-agonists, theophylline, caffeine, steroids, valproic acid, amiodarone, antiarrythmics (e.g., mexiletine, procainamide), calcitonin, levothyroxine, chemotx, immunosupps (tacrolimus, cyclosporine), cocaine, amphetamines	Taper/eliminate drug if possible Clonazepam (start 0.5 mg, increase gradually) Propranolol (10-40 mg/day)

Myoclonus	opiates, Ca-channel blockers, TCAs/SSRIs, lithium, neuroleptics, anticonvulsants, levodopa, bromocriptine, pseudoephedrine, tryptophan, B-agonists, physostigmine, EtOH	Taper/eliminate drug if possible Clonazepam (start 0.5 mg, increase gradually) Keppra (start 250-500 mg/day, range 1000-3000 mg/day) Valproic acid (start 125 mg bid, range 10-15 mg/kg/day) Also check for uremia, liver dysfunction, electrolyte abnormalities, and glucose abnl
Tardive drug-induced movement disorders		
Hyperkinetic (dystonia, chorea/dyskinesia, tics, myoclonus, akathisia)	Typically DA-blocking antiemetics and antipsychotics	Taper/eliminate drug if possible Tetrabenazine Clonazepam Quetiapine, clozapine Anticholinergics, baclofen, or tizanidine for dystonia Propranolol for akathisia Botulinum toxin for focal dystonia Deep brain stimulation in resistant cases

NEUROLEPTIC MALIGNANT SYNDROME

- call hotline for assistance: (888) 667-8367

- Risk Factors: Complication of exposure to D2-receptor blockers (neuroleptics > antiemetics); also described in lithium exposure and rapid elimination of dopaminergic meds in Parkinson's
- Epi: Occurs anytime (usually in 1st 3-9 days), incidence 0.5-2.4% exposed, mortality 4-20%
- Sx: Hyperthermia, autonomic dysfunction, altered mental status, bradykinesia, muscular rigidity
- Dx: Leukocytosis and increased CK levels
- Tx: A) Supportive: Remove agent, aggressive IV fluids/diuresis, BP support, temp control
  B) Meds: Bromocriptine 5 mg QID vs Dantrolene 3-5 mg/kg IV divided 3-4x/d

Table 2 Potential culprits or causes of drug-induced parkinsonism (DIP)

High risk	
Dopamine D2-receptor blockers	Neuroleptics: butyrophenones[3] (haloperidol and others), phenothiazines[3] (prochlorperazine), thioxanthenes[3] (thiothixene), dibenzoxazepine[3] (loxapine), others
	Atypical neuroleptics: risperidone[3] (especially in higher concentration)
	Antiemetics/gastric motility agents: substituted benzamides[1,3] (metoclopramide, prochlorperazine, and others)
Dopamine depleters	Tetrabenazine[3]
Antihypertensive agents thought associated with DIP by reducing dopamine levels	Reserpine and alpha-methyldopa[1,3]
Intermediate risk	
Calcium channel blockers with dopamine antagonist activity	Flunarizine,[1,3] cinnarizine,[3] verapamil[1]
Certain anticonvulsants	Valproate[3*]
Mood stabilizer	Lithium[3] (causes tremor and myoclonus)
Atypical neuroleptics	Risperidone,[3] clozapine,[5] and others(especially in higher dose)
Lower risk*	
Antihypertensives	Diltiazem,[3] captopril[3]
Antiarrhythmic	Amiodarone,[1,3] procaine[3]
Immunosuppressants	Cyclosporine,[1,3] tacrolimus[3]
Antidepressants	Fluoxetine[3] (and other SSRIs), tricyclic antidepressants,[3] and certain MAOIs, e.g., phenelzine[3]
Antifungals	Co-trimoxazole, amphotericin B[3]
Antibiotics	Trimethoprim-sulfamethoxazole[3]
Antivirals	Vidarabine, acyclovir (and antiretroviral drugs for HIV)[3]
Chemotherapeutics	Thalidomide, cytarabine, ifosfamide, vincristine, tamoxifen, and cytosine arabinoside[1,3]
Statins	Lovastatin and others[1,3]
Hormones	Levothyroxine,[3] medroxyprogesterone,[3] epinephrine[3]
Others	Bethanechol,[3] pyridostigmine,[3] donepezil[3]

*There are anecdotal reports of tremor associated with some newer anticonvulsants, though parkinsonism was not described. Examples are tiagabine, gabapentin, oxcarbazepine monotherapy, and lamotrigine.[3]

†Medications that rarely can cause or worsen parkinsonism and tremor.

MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor.

Movement Disorders Suggested Reading:

Jankovic J. Parkinson's disease: Clinical features and diagnosis. Journal of neurology, neurosurgery, and psychiatry. 2008;79:368-376.

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NEUROCRITICAL CARE

Special thank you to Dr. Levine and Benjamin Abella for their assistance in editing this section for the 2022-2023 guide.

For further reading please see Neurocritical care website for resources and protocols: **https://www.med.upenn.edu/ncc/secure/**

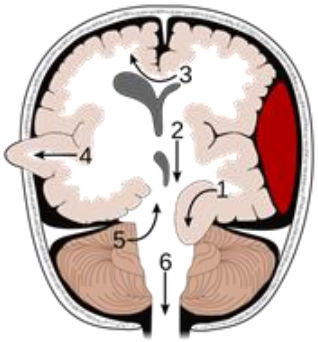
Managing elevated ICP

Basic Physiology: The skull has a fixed volume, so any increase in the volume of one of the components (blood, CSF, parenchyma) will lead to an increase in ICP (this is the Monro-Kelli hypothesis). Some measures can be taken to reduce the volume of other intra-cranial components, but unless the underlying issues is fixed eventually the increased ICP will lead to severe consequences:

-Reduced cerebral perfusion pressure (Cerebral perfusion pressure = MAP-ICP)
-Herniation of the brain, compression of the brainstem, and eventual death

Note that the absolute ICP number is not as important as the rate of the ICP rise – somebody with a slowly increased ICP may have minimal symptoms but someone with a slightly increased ICP who normally lives in the normal range can herniate if the increase is acute.

Symptoms of elevated ICP: headache, diminished level of consciousness, cranial nerve palsies (CN VI), impaired upgaze, Cushing's response – brady, elevated BP, respiratory depression.



Herniation Syndromes:

1. UNCAL HERNIATION

- Decreased level of arousal, abnormal posturing, dilated non-reactive pupil ipsi to lesion (ipsi CN III compression)
-Contralateral hemiparesis (occasionally ipsi hemiparesis if compress contralateral cerebral peduncle-Kernohan's notch or "false localizing sign")
-PCA compression with contra homonymous hemianopsia

2. CENTRAL (DIENCEPHALIC) HERNIATION

- Early: Somnolence, small pupils, flexor posturing, Cheyne Stokes breathing
>>>Hypothalamic sympathetic nuclei compression mioitic pupils w/ impaired upgaze ("sunset eyes")
>>> III nerve(s)/nuclei compression dilated pupil(s) w/wo fixed position
>>>Basilar perforator shearing (Duret hemorrhages) fluctuating consciousness, decorticate rigidity, Cheyne Stokes respirations
>>>Obstruction of foramen of Monro intracranial hypertension (headache, nausea/vomiting, fluctuating consciousness)
-Intermediate: Coma, mid-sized fixed pupils, hyperventilation, extensor posturing
-Late: Loss of oculocephalic and oculovestibular reflexes, ataxic breathing

3. CINGULATE (SUBFALCINE) HERNIATION

- *Most common type of herniation syndrome*
- Headache is the most common symptom
- ACA compression new ipsilateral, contralateral, or bilateral bilateral lower extremity weakness/plegia

4. TRANSCALVARIAL HERNIATION

- Varies anatomically with location of injury
- Be wary of subdural hematomas that may grow from recent trauma

5. INFRA-to-SUPRATENTORIAL HERNIATION (UPWARD)

- Can present the same way as a diencephalic herniation
- Often occurs simultaneously with tonsillar herniation
- A risk with a large posterior fossa mass/bleed, if supratentorial decompression or EVD was placed

6. TONSILLAR HERNIATION

- Compression of medullar respiratory centers Sudden cardiopulmonary arrest, lower cranial nerve dysfunction

-Progression of respiratory arrest over several days, can see Apneustic breathing (deep gasping inspiration with pause followed by incomplete exhalation, pons) ataxic breathing (irregular pattern with intermittent apnea, medulla) Midbrain/pontine separation from basilar artery (Duret hemorrhages into brainstem) Decorticate posturing, Kussmal's breathing, respiratory arrest, fluctuating attention death

Measures to reduce ICP:

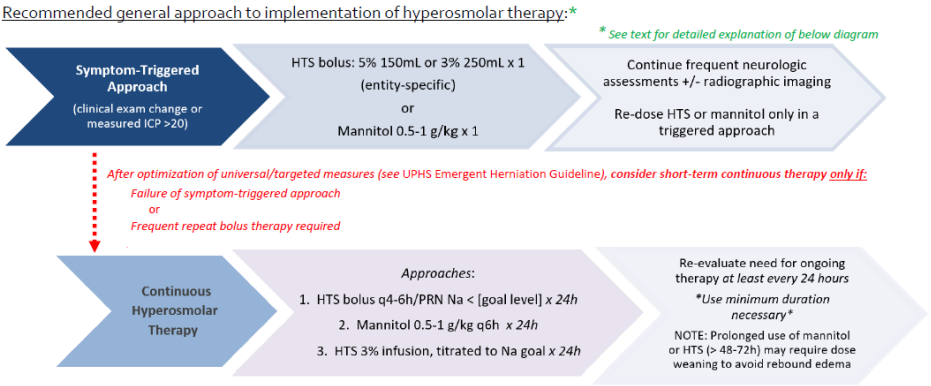
- CSF drainage reduce CSF volume
- Hyperosmolar therapy reduce brain tissue edema/brain tissue volume
- Hyperventilation causes vasoconstriction reduced blood compartment and therefore reduces cerebral blood volume – *this effect is transient and can lead to rebound cerebral blood flow (do this as a bridge to something definitive, like a hemicrani)*
- Metabolic therapy like barbiturate coma reduces cerebral metabolic rate which can reduce cerebral blood flow and volume
- Craniectomy increases the volume of the cranium (used in malignant MCA strokes or large cerebellar strokes which allows the edematous dead tissue to expand outward)

Stepwise management of acute intracranial hypertension Note: Please see full pathway on Dorsata/PennPathway (https://pathways.dorsata.com/)

Universal measures

- HOB elevated above 30 degrees
- Maintain head facing straight, see if C collars can be exchanged for bolsters to stabilize C spine – goal here is to maximize jugular venous drainage
- Avoid hypotonic fluids
- Adequate sedation, avoid fevers, treat seizures in order to minimize CNS metabolic demands
- Consider ICP monitoring (patients generally would be in NICU if this is undertaken)
- Treat elevated intra-abdominal/intrathoracic pressure
- *If there will be definitive therapy can do short term hyperventilation* for goal PaCo2 30-35 – use for less than 2 hours due to excessive vasoconstriction and rebound increased cerebral blood flow

Hyperosmolar therapies



Choosing between mannitol/hypertonic saline depends mainly on patient specific factors (see below), as there aren't clear differences in outcomes between the two agents.

-**Mannitol**: complications include hypovolemia and hypotension as mannitol will cause osmotic diuresis, electrolyte imbalances, AKI. Relative contraindications include renal failure/hypovolemia

To give Mannitol: NOTE: See mannitol checklist below

1. Give Mannitol 20% 0.5-1 g/kg bolus; maximum 100g
2. Check serum osmolality and basic chemistry in 4-6 hours to calculate Osm Gap (in case re-dosing is needed):

a. Osm Gap = (measured serum osm – [2 x serum Na + Glc/18 + BUN/2.8])

3. Diuresis lasts ~2-3 hours post-dose – replete urinary volume loss as needed per patient's volume status
    a. e.g., if baseline hypervolemia, may be appropriate to replace 0-50% of measured UOP
    b. Mannitol administration is not an absolute indication for a Foley – can consider IUC if suspected urinary retention or if frequent mannitol dosing

-**Hypertonic Saline (HTS):** complications include volume overload/pulmonary edema and is therefore is relatively contraindicated with CHF, as well as acidotic patients to avoid chloride load.

5% bolus therapy

1. Obtain stat BMP for serum Na if none available in last ~6-12 hours
2. Bolus 150 mL 5% NaCl IV over 10 minutes (unless suspicion for current serum Na >160, no need to wait for labs to return before giving the bolus)

3% infusion therapy

1. Can be considered as a last line if refractory/recurrent ICP elevations if bolus 5% HTS or mannitol are ineffective

Mannitol Overview – Checklist

Dose: 0.5 – 1 g/kg (usual max 100 grams)

Relative contraindications:
- Hypovolemia
- Severe hemodynamic instability
- Renal failure

Administration:
- ❑ CVC preferred; Peripheral IV ok if no CVC
- ❑ Requires filter (≤ 5 micron)
- ❑ 20% pre-mix (500 mL): via Alaris pump
- ❑ 25% vials: IV push (use disk filter)

Monitoring:
- ❑ Blood pressure & urine output x 2-3hrs
  - ❑ Replete volume loss PRN (IV fluids) according to patient's volume status
- ❑ Send BMP + SOsm (4-6 hrs after dose)
  - ❑ → calculate Osm gap
  - ❑ Replete electrolytes (K^+, Mg)

Repeated administration:
- ❑ Re-dosing interval – up to every 4-6h if clinical condition requires
- ❑ Calculate Osm gap **prior to** giving another dose:
  - ❑ If <15, send BMP + SOsm before *every other* dose
  - ❑ If ≥15, send BMP + SOsm *prior to each dose*
- ❑ HOLD mannitol if Osm GAP >20, unless urgent clinical condition warrants

HTS Bolus Overview – Checklist

Dose: **5%**, 150 mL (7.5 g) *(HUP/PPMC)*
or **3%**, 250 mL (7.5 g) *(other entities)*

Relative contraindications:
- Significant volume overload
- Severe CHF
- Chronic hyponatremia
- Current serum Na > 155 mEq/L

IV Access:
- ❑ CVC preferred if available
- ❑ Peripheral IV administration permitted for max 48 hrs; further use → must place CVC

Monitoring:
- ❑ Send BMP 2-4 hrs after dose, or schedule BMP q4-6 hrs if anticipating ongoing bolus therapy

Repeated administration:
- ❑ Re-dosing interval – up to every 4-6h if clinical condition requires
- ❑ May schedule BMP q4-6 hrs if anticipating ongoing bolus therapy
- ❑ HOLD if serum Na > 160, unless urgent clinical condition warrants

3% HTS Infusion Overview – Checklist

Dose: HTS 3%, 10-100 mL/hr
- ❑ Usual starting rate: 20-50 mL/hr
- ❑ Titration (provider-directed): ↕ by 10-20 mL/hr q4-6h

Relative contraindications:
- Significant volume overload
- Severe CHF
- Chronic hyponatremia
- Pre-therapy serum Na > 155 mEq/L

IV Access:
- ❑ CVC preferred
- ❑ Peripheral IV administration permitted for short-term use (up to 48 hours)

Monitoring:
- ❑ Serum sodium (via BMP) q4-6h while on infusion
- ❑ HOLD infusion if serum Na > 160

Other measures

Decompressive Craniectomy: definitive therapy for severe intracranial hypertension (especially consider for acute ischemic stroke with malignant brain swelling). Most studies have demonstrated a reduction in mortality in malignant MCA syndrome (see DECIMAL, DESTINY, HAMLET; not HeADDFIRST) but effect on functional outcomes is more controversial (see HAMLET and DECIMAL). A significant proportion of patients who get DHC and survive have Modified Rankin Scales (MRS) of 3 or better (able to walk without assistance). However, a significant proportion of patients who get DHC and survive have MRS of 4 or worse (unable to walk, dependent on others for assistance with bodily needs). Left versus right hemispheric stroke does not impact outcome. Only used in select TBI cases when medical management fails (see controversial DECRA and RESCUEicp trials).
CSF Drainage: Consider ventriculostomy for monitoring and controlling ICP when appropriate.
Hypothermia: a last tier treatment, not likely to improve outcome but does reduce ICP (see POLAR-RCT trial for TBI). For TBI, goal is to avoid fevers (i.e. normothermia).
Barbiturate coma: Has been used for medically refractory increased ICP usually in the setting of SAH or head injury.

Different forms of physiological monitoring

DEVICE	ADVANTAGES	DISADVANTAGES
Ventriculostomy (EVD)	Provides direct and continuous measurement of ICP, Can drain CSF when ICP rises	Invasive, Moderate bleed risk, 10% infection risk

Intraparenchymal Probe (Bolt, Camino)	Less invasive	Less accurate than EVD, Cannot drain CSF, Moderate bleed risk
Brain Tissue Oximetry (Licox)	Measures local oxygenation, Detects early ischemia (goal PbO2 >15mmHg)	Only detects local ischemic changes
Microdialysis Catheter	Quantitates local metabolites (lactate, glutamate, pyruvate). Dangerous levels: lactate > 2.5 mmol/L, LPR > 25, glucose < 2 mM, and glutamate >20 μmol/L	Only detects local metabolic changes
Jugular Bulb Catheter	Measures JVO2 saturation, when compared to SVO2 it can suggest global ischemic changes	May miss focal or small areas of ischemia
Continuous EEG	Detects subclinical seizures & early ischemia or hemorrhage. Can be via scalp EEG or depth electrode.	Requires you or EEG fellow to read. Depth electrodes record from small areas.
Electrocorticography (ECoG)	AKA intra-operative intracranial electroencephalography, uses electrodes placed directly on the exposed surface of the brain to record electrical activity	Requires a trained technician or EEG fellow to read
Xenon CT	Quantitates CBF in multiple areas	Currently a research tool

Of note: if you see an ED consult for TBI at PPMC or a patient in clinic who could benefit from TBI clinic referral*:

1. Be sure to include TBI clinic in their dotphrase (if consult)
2. Provide the patient with the TBI clinic number (same as general neurology clinic): 215-662-3606
3. Send Epic message to Megan Moore, MSN, ANP-BC for assistance with scheduling

*They have a dedicated neuropsychiatrist

Anoxic brain injury and therapeutic hypothermia

One of the most common Neurology consults is to provide a neurological prognosis following cardiac arrest. Our ability to give the primary team and the family as clear guidance as possible depends on several factors, which this section of the guide will highlight. Many times we won't be able to give a clear cut answer, but we can still help the family make decisions based on most likely scenarios.

Therapeutic hypothermia (TTM) for cardiac arrest

TTM improves outcomes following a cardiac arrest by:

1. Decreases cerebral metabolism (6-10% reduction for every 1C reduction in core temp)
2. Decreases amounts of free radicals/cytotoxic cascades
3. Diminishes blood brain barrier degradation and cerebral edema

Five RTCs have been performed on TTM and neurological outcome and survival, with the initial 2 studies showing a number needed to treat of 6 for good neurological outcomes (meaning the person is at least able to work in a sheltered environment and is independent in ADLs. A 2016

Cochrane review found moderate quality of evidence that TTM produces good neurological outcomes versus no cooling.

UPHS TTM pathway

NOTE: please see the full pathway on PennPathway – included below are just some key points for reference

Eligibility criteria

Table 1: TTM Inclusion and Exclusion Criteria

Inclusion Criteria	● Remains comatose immediately following out-of-hospital or in-hospital cardiac arrest with return of spontaneous circulation, regardless of initial cardiac rhythm
Exclusion Criteria	● GCS (motor) = 6 and patient following commands ● Severely impaired pre-arrest cognitive status e.g. advanced dementia ● Persistent non-perfusing cardiac rhythm or ongoing refractory shock despite interventions ● Code status active for no resuscitation/intubation

Determining temperature goals

- Target temperature of 33C is recommended for most patients based on injury severity and should be achieved within 4 hours of ROSC and maintained for 24 hours before rewarming
- Target temperature of 36C (or device-controlled normothermia at 37C, see below) may be preferred if patient has known significant bleeding from recent surgery, trauma or has significant long QT on ECG (history of bleeding or anticoagulant use is not a contraindication to management at 33C)

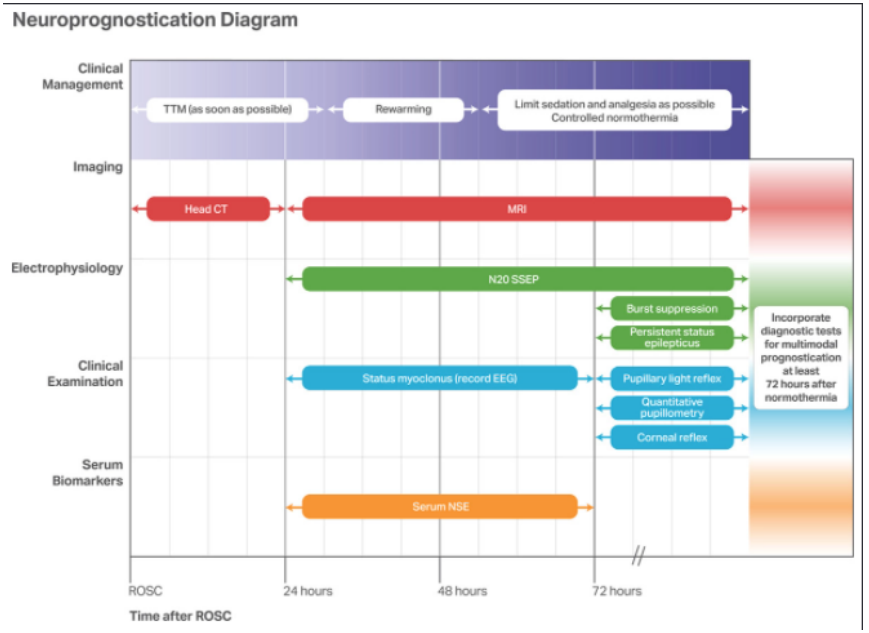
NOTE that it is not clear if 33C or 36C is superior – this remains an issue of clinical judgment. Studies showing equivalence of management at 36C or even 37C involved cohorts with very high rates of witnessed arrest and delivery of bystander CPR as well as low prevalence of shock – if a Penn post-arrest patient fits these criteria with low risk of neurologic impairment, 36C or 37C may be appropriate as a temperature goal.

The earliest RTCs used temps between 32C and 34C, but the Therapeutic Temperature Management Trial that came after did not find a difference between 33C and 36C, and a newer trial (TTM2) found no difference between 33C and fever prevention (<37.8C). However, in 2017 a center in Australia reported worsening clinical outcomes after they switched from 33C to 36 C. A similar finding was reported from Seattle in 2019, with worsened outcomes after a switch at 36C. Newer studies have provided insights into this controversy, finding that TTM does not appear to improve outcomes with mild post-arrest injury, but appears to improve outcomes with moderate post-arrest injury. Thus, patient selection is key.

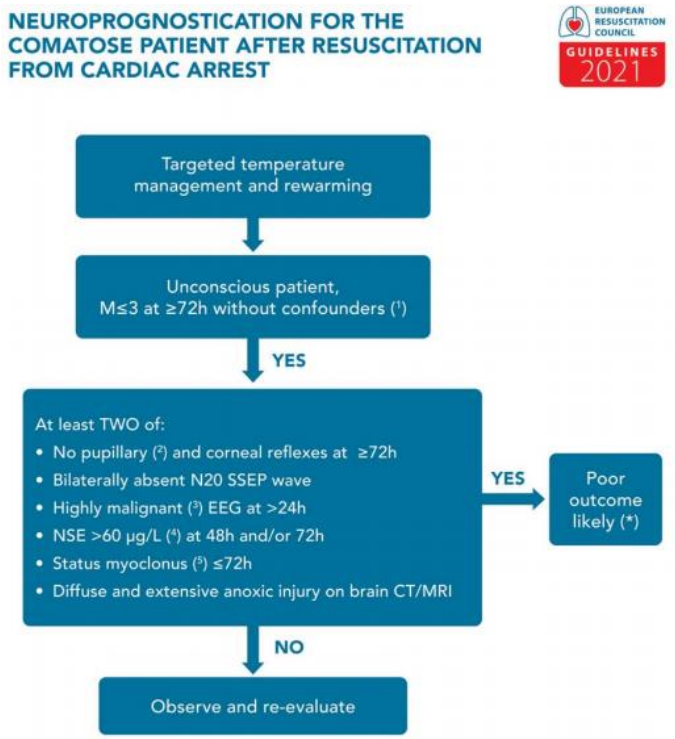
EEG monitoring

- EEG monitoring is started within 6-12 hours after TTM initiation (does not require overnight connection or Neurology involvement). LTM continued through TTM and 24 hours after rewarming. Neurology consult team can be involved if seizures/epileptiform abnormalities are discovered).

Prognosticating after cardiac arrest



American Heart Association 2020 guidelines on neuroprognostication following cardiac arrest



Notes for European Rescucitation Council 2021 guidelines

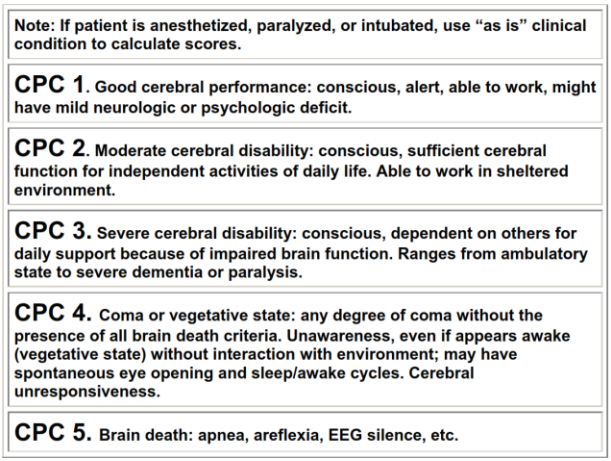
1.Major cofounders include paralytics, hypothermia, sedation, sepsis…
2. Use automated pupillometer when possible
3.Malignant EEG = suppressed background +/- periodic discharges or burst suppression (not from sedatives)
4.Increasing NSE levels between 24-48h or 24/48 and 72h further support poor outcome
5.Defined as continuous and generalized myoclonus persisting for 30 minutes or more.
*Use caution in cases where there are discordant signs, some showing bad outcome and some showing good outcome.

Neuroprognostication After Cardiac Arrest

You will often be consulted to predict neurologic outcomes for comatose patients after cardiac arrest. While there is no single test that predicts these outcomes with 100% sensitivity and

specificity, there are evidence-based tools that can (and should) be used in combination to help inform these predictions.

Providing families with a neurological prognosis following cardiac arrest involves integrating several pieces of data beginning within the first 24 hours of hospitalization and extending several days after a patient is re-warmed. There is no one correct way to proceed with a workup to provide a prognosis, but included above are two different flowcharts from recent professional society guidelines for reference. Generally when these societies reference a "poor prognosis" they are referring to a CPC score of 3-5 (see below). Note that I did not include the AAN 2006 guidelines, as these are out of date.



Safar P. Resuscitation after Brain Ischemia, in Grenvik A and Safar P Eds: Brain Failure and Resuscitation, Churchill Livingstone, New York, 1981; 155-184.

Categories 1 and 2 considered the good outcomes in most studies

Clinical Examination: pupil examination during the first 72 hours after cardiac arrest is highly specific but not completely sensitive for poor neurologic outcome at 3 months, and quantitative pupillometry (NPi ≤ 2) increases this specificity [1]. Lack of localizing motor response to pain also represents a poor prognosis.

> NOTE: we typically allow at least 48 hours after sedation wean and 72 hours after rewarming to be more firm in utilizing lack of localizing motor response or pupil reactively/corneal reflex. Also note that pupils/corneals are currently favored by professional guidelines over the motor response.

Imaging: Grey-white differentiation as measured by grey-white ratio (GWR) is specific but not sensitive for poor outcome. MRI is more sensitive but has a higher false positive rate, and the ideal timing of MRI after cardiac arrest is unclear [2], and is often difficult to obtain, but if possible should be obtained between days 5-10 post-arrest.

EEG: Patients undergoing TTM have LTM as part of the TTM protocol. Patterns including generalized suppression (highly specific, susceptible to medication effects), burst-suppression with identical bursts (highly sensitive within 48h of ROSC, variable bursts may be medication effect) portend a poor prognosis, while other patterns including continuous background and rhythmic delta activity may be associated with good outcomes (though with poor sensitivity and specificity) [3].

SSEPs: Absence of N20 bilaterally is one of the most reliable predictors of poor outcome available; case reports of patients with good neurologic outcomes despite absent N20 bilaterally exist but have been called into questions on methodological grounds [4].

NOTE 1: that SSEPs can only be interpreted when the patient has intact peripheral nerves/cervical spinal cord (i.e. somebody with a severe axonal neuropathy simply won't show any propagation of the response after the median nerve is stimulated. *To be useful for neuroprognostication you will either see present N20's or you will see response propagate to spine/brainstem and then stop (absent N20s).*

NOTE 2: while not impacted by sedatives, there have been cases of early false positives (within 1 day of arrest). It is best to perform SSEPs after rewarming has been completed – day 2/3.

NOTE 3: while lack of N20 response bilaterally is specific for a poor outcome, presence of N20s does not mean the patient will have a good neuro outcome – must take other tests into account!

Neuron-specific enolase (NSE): While other serum biomarkers are being evaluated, elevated NSE is currently the most reliable serum-based predictor of poor outcome in clinical use. A ratio of NSE at 24h and 48h after ROSC ≥ 1.0 (reflecting increasing levels over time) increases the specificity of the study and avoids interpretation issues related variable value ranges from different labs [5]. There is no current standard cutoff for this test that reliably predicts poor outcome, although numbers from the 40s-60s have been proposed in meta-analyses.

NOTE: in my experience (MB) this test can take some time to come back (in 1 patient it took a week).

Consult Protocol for RECOVER service (Neurology consult service for neuroprognostication post-cardiat arrest):

1. Gather HPI including time to CPR, time to ROSC, time to TTM, and pre-arrest neurological baseline
2. Examine the patient and obtain quantitative pupillometry
3. Recommend the above studies to inform the prognostic picture (use the RECOVER consult note: RECOVERNOTECARDIACARREST from Dr. David Fischer's smartphrases)
   - Serial neurologic examinations (at least daily), including quantitative pupillometry
   - CT head when able, preferably within 72 hours of arrest
   - maintain continuous EEG
   - obtain median nerve SSEPs
   - Send neuron-specific enolase (NSE) at 24 hours and again at 48 hours post-arrest
   - Obtain MRI Stroke protocol when able (*suggest this as it is a shorter protocol that gives a decent sense of structural problems)*

Additional Resources

1. Oddo M, Sandroni C, Citerio G, Miroz JP, Horn J, Rundgren M, Cariou A, Payen JF, Storm C, Stammet P, Taccone FS. Quantitative versus standard pupillary light reflex for early prognostication in comatose cardiac arrest patients: an international prospective multicenter double-blinded study. Intensive Care Med. 2018 Dec;44(12):2102-2111.
2. Lopez Soto C, Dragoi L, Heyn CC, Kramer A, Pinto R, Adhikari NKJ, Scales DC. Imaging for Neuroprognostication After Cardiac Arrest: Systematic Review and Meta-analysis. Neurocrit Care. 2020 Feb;32(1):206-216.
3. Muhlhofer W, Szaflarski JP. Prognostic Value of EEG in Patients after Cardiac Arrest-An Updated Review. Curr Neurol Neurosci Rep. 2018 Mar 10;18(4):16.

4. Rothstein TL. SSEP retains its value as predictor of poor outcome following cardiac arrest in the era of therapeutic hypothermia. Crit Care. 2019 Oct 23;23(1):327.
5. Chung-Esaki HM, Mui G, Mlynash M, Eyngorn I, Catabay K, Hirsch KG. The neuron specific enolase (NSE) ratio offers benefits over absolute value thresholds in post-cardiac arrest coma prognosis. J Clin Neurosci. 2018 Nov;57:99-104.

Managing the ICU patient (i.e. things you forgot from intern year)

The Mechanical Ventilator

Basic purposes for mechanical ventilation are to be provide the patient with adequate VENTILATION (removal of carbon dioxide) and OXYGENATION (provision of oxygen). Initiation of breaths can be pressure-triggered (e.g. -1 or -2 cm H2O) or flow-triggered (e.g. 2L/min), after which air can be delivered using a preset pressure (e.g. pressure-support) or volume (volume-cycled).

Tidal Volumes: start 6-8 cc/kg/min of predicted body weight in all comers, 4-6 cc/kg/min of predicted body weight for patients with acute lung injury/ARDS (PaO2/FiO2 ratio <300; monitor for hypercapnia).

Troubleshooting the Vent

1.Respiratory distress: bucking, tachycardia, anxiety, paradoxical breathing, flaring of nostrils
- *DDx:* ET malfunction (kinked, clogged, leaking); inappropriate vent settings; bronchial obstruction (mucus plugging); bronchospasm; auto-PEEP in pts with high RR; pulmonary embolism; pulmonary edema; pneumonia; pneumothorax; anxiety/pain
- *Initial management if patient is unstable:* disconnect from the vent and ambu-bag with 100% O_2 - if status improves consider inadequate vent settings as the culprit; check ET tube for air-leak/patency (with suction cath); assess for symmetric breath sounds/wheezing; CXR; ABG

2. Breath stacking: switch to pressure support or increase sedation

3. Elevated peak airway pressures:
- *DDx*: vent probs: excessive Vt, inspiratory time too short, fluid in circuit; ET tube: plugging or kinking, endobronchial intubation; bronchospasm; ptx; lobar collapse from plugging

4.Desaturation:
- *DDx:* endobronchial intubation, pneumothorax, pulmonary embolism, ARDS, pulmonary edema, pneumonia, atelectasis, mucus plugging

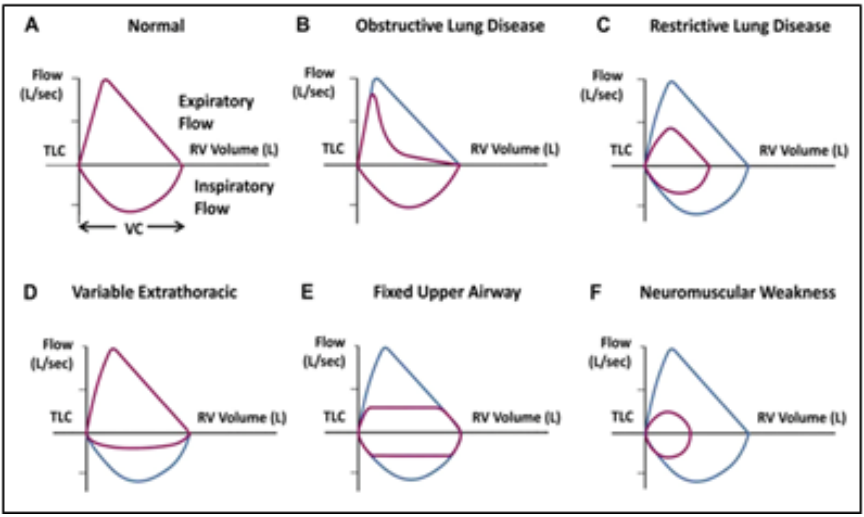
5.Low exhaled volumes: check for cuff leak

6.High minute ventilation: inadequate sedation, metabolic disturbances, incorrect vent settings, ↑dead space

VENTILATOR MODE	FIXED PARAMETERS	ADJUSTABLE PARAMETERS	ADVANTAGES	DISADVANTAGES
(Synchronized) Intermittent Mandatory Ventilation	Volume-cycled (same volume delivered, e.g. 6 cc/kg/min)	Back-up RR	- Permits spontaneous breathing - Reduces risk of "auto-peep"-ing (which can impair cardiac output) & ventilator-induced lung injury	- Requires patients to be alert enough to trigger breaths - Increases work of breathing (the ventilator is a high resistance circuit) - Reduces cardiac output

			Avoid in neuromuscular disease & heart failure	
Pressure Support	Pressure-cycled (same pressure delivered for each initiated breath, e.g. -5 cm H2O)	Pressure (patient controls RR, TV, inspiratory time & flow rate)	- Alert patients won't "buck" the vent - Most physiologic mode (augments spontaneous breathing) ***Preferred mode during ventilatory weaning*	- Requires patient to be alert enough to trigger breaths
Pressure Controlled	Pressure-cycled		- Decelerating flow rate w/ inspiration reduces peak airway pressure ***Avoid in ARDS d/t low lung compliance*	- Inflation volumes vary
Assist-Control	Volume-cycled	TV, Back-up RR, flow rate	- Most common mode for comatose/paralyzed patients - No trigger needed to initiate breath, but trigger can be used ("assisted") ***Preferred mode following intubation*	- Alert patients may "buck" the vent - Lower TV risks atelectasis - Higher TV risks ventilator-associated lung injury & "auto-peep"-ing

Selected Flow-Volume Loops



Acid, Bases, and Metabolic Disturbances

ABG RESULT	Interpretation	MATH	VENTILATOR ADJUSTMENT
pH <7.35	Acidemia	Determine if metabolic (e.g. lactic acidosis, hyperchloridemia) or respiratory (e.g. insufficient ventilation such as COPD)	Treat underlying cause
pH >7.5	Alkalemia	Determine if metabolic (e.g. milk-alkali syndrome) or respiratory (e.g. hyperventilation)	Treat underlying cause
PaCO2 <35 mmHg	Acute respiratory alkalosis	Dec. in HCO3 = 2(ΔPaCO2/10)	Reduce RR, TV
	Chronic respiratory alkalosis	Dec. in HCO3 = 5(ΔPaCO2/10) to 7(ΔPaCO2/10)	

PaCO2 >45 mmHg	Acute respiratory acidosis	Inc. in HCO3 = ΔPaCO2/10	Increase RR, TV
	Chronic respiratory acidosis	Exp. PaCO2 = 3.5(ΔPaCO2/10)	
		**if HCO3 or PaCO2 not what you're expecting, there are likely 2 independent processes occurring*	
PaO2 <90 mmHg	Hypoxemia		Increase FiO2, PEEP
PaO2 >110 mmHg	Hyperoxemia		Reduce FiO2, PEEP
HCO3 <22 mg/dL	Metabolic acidosis	Exp. PaCO2 = 1.5(HCO3) + 8 ±2	Treat underlying cause
HCO3 >30 mg/dL	Metabolic alkalosis	Inc. PaCO2 = 40 + 0.6(ΔHCO3)	Treat underlying cause

pH Imbalance Differential

Respiratory Acidosis	**Respiratory Alkalosis**
Airway Obstruction	*Hypovolemia*
COPD	GI H+ losses (vomiting, gastric suction, diarrhea)
Asthma	Renal H+ losses (loop diuretics)
Mucus plug/aspiration	*Hypervolemia*
CNS depression	Renal H+ losses (CHF, nephrotic syndrome, cirrhosis, steroids, hyperaldo-, hypercortisolism)
Sleep-disordered breathing	
Neuromuscular weakness	

Hyponatremia

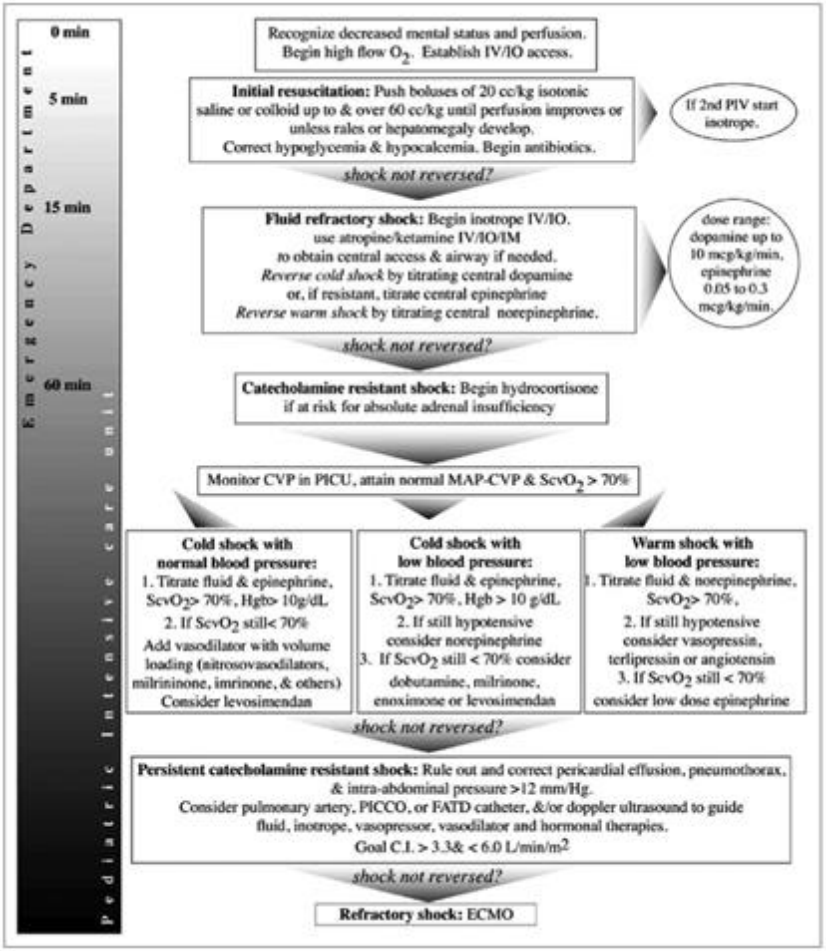
HYPOVOLEMIC	**HYPERVOLEMIC**	**EUVOLEMIC**
Extrarenal loss (urine Na<30) Burns, sweat, GI loss, pancreatitis	Urine Na<30 CHF, cirrhosis, nephrotic syndrome	SIADH *(to distinguish from salt wasting, look at UOP which is high in salt wasting)*
Renal loss (urine Na>30) Diuretics, Na-wasting nephropathy, cerebral salt wasting (common in SAH), Mineralocorticoid deficiency (often associated with ↑K)	Urine Na>30 Chronic Renal Insufficiency	Hypothyroidism, Adrenal Insufficiency, water intoxication

TREATMENT		
Volume expansion with 0.9% NaCl or NaCl tabs.	Correct underlying cause, can use demeclocycline	chronic, asymptomatic: fluid restriction < 1L/day; demeclocycline if not improving
Acute, symptomatic (Na<120) – 3% NaCl, correct no faster than 0.5 mEq/hr (goal Na~125 & then switch to conservative measures).		

Hypernatremia

HYPOVOLEMIC	**HYPERVOLEMIC**	**EUVOLEMIC**
Skin losses, GI losses, diuretics, renal disease, hyperosmolar non-ketotic hyperglycemia, mannitol	Iatrogenic (hypertonic fluids, tube feeds, dialysis)	Polyuria (>300cc dilute urine/hr): Diabetes insipidus (central, nephrogenic)
		Decreased free water intake, fever, mechanical ventilation
TREATMENT		
Volume resuscitation with 0.9% NaCl, replace free water deficit with D5W or other hypotonic fluids with goal of ↓ serum Na by 0.5 mEq/hour	Replace free water deficit with D5W or other hypotonic fluids with goal of ↓ serum Na by 0.5 mEq/hour	If central DI: replace ongoing urine losses mL per mL with D5W or ¼ NS, administer ddAVP intranasal (10-20mcg) or oral (0.25 – 0.5mg). Monitor rate of correction.

Septic Shock



NEUROCRITICAL CARE

Causes of Shock

TYPE	ETIOLOGIES	SIGNS/SX	CVP	CO	PCWP	SVR
Distributive	Sepsis, anaphylaxis, neurogenic, adrenal insufficiency	"warm shock" w/ hyperemia	☐	☐	nml/☐	☐
Hypovolemic	Blood loss, dehydration, GI losses, third spacing, insensible losses (hyperventilation, fever)	cool clammy skin, concentrated urine, oral membranes, dec. skin turgor	☐	☐	☐	☐
Cardiogenic	MI, valve prolapse, tamponade, PTX, arrhythmia	cool skin, elevated JVP, crackles, EKG changes	☐	☐	☐	☐

Rough properties of various vasopressors

Drug Typical dose range	Target	Effect on - Heart rate - Inotropy - Ectopy	Effect on systemic vascular resistance	Effect on cardiac output	Effect on blood pressure	Effect on pulmonary vascular resistance	Main uses	Safe for peripheral use?
Inodilators								
Dobutamine 2-20 mcg/kg/min	αββββ	⇑⇑⇑	⇓	⇑⇑⇑	Variable	⇓	Cardiogenic shock	
Milrinone 0.375-0.75 mcg/kg/min	cAMP	⇑⇑⇑	⇓⇓	⇑⇑⇑	Variable	⇓⇓	Cardiogenic shock	
Isoproterenol 2-10 mcg/min	ββββ	⇑⇑⇑⇑⇑	⇓	⇑⇑⇑	Variable		Bradycardia	Yes
Pure Vasopressors								
Vasopressin 0.01-0.06 U/min	V1 & V2	⇓	⇑⇑⇑	⇔/⇓	⇑⇑⇑	⇓	Distributive shock, Pulmonary HTN	No.
Phenylephrine 40-180 mcg/min	αααα	⇓	⇑⇑⇑	Variable	⇑⇑⇑	⇑⇑	Distributive shock	Yes
InoPressors								
Norepinephrine 0-40 mcg/min*	αααβ	⇑	⇑⇑⇑	⇔/⇑	⇑⇑	⇔	Shock (most types)	Yes, for short period with monitoring
Epinephrine 0-20 mcg/min*	αββββ	⇑⇑⇑	⇑	⇑⇑⇑	⇑⇑		Bradycardia, cardiogenic shock, sepsis, anaphylaxis	Yes
Dopamine, low 1-4 mcg/kg/min	Dopa-R	⇔	⇓	⇑	⇓		Zombie apocalypse (absence of better agents).	Probably not
Dopamine, medium 4-10 mcg/kg/min	αββββD	⇑	Variable	⇑⇑	Variable			
Dopamine, high 10-20 mcg/kg/min	αααβD	⇑⇑	⇑⇑	⇑	⇑⇑⇑	⇑		

*Listed ranges are typically used doses in the United States, but there is no true "maximal" dose. Some countries may tend to use higher doses than others. At very high doses, pressors may lose some receptor specificity. The best dose is the dose required to keep the patient alive – in some cases very high norepinephrine or epinephrine doses may be needed. -*The Internet Book of Critical Care, by @PulmCrit*

NEURO-ID
MENINGITIS/ENCEPHALITIS

MENINGITIS	ENCEPHALITIS
S/S: HA, photophobia, phonophobia, meningismus, N/V, fever, malaise, irritability - signs may be minimal in immunocompromised patients	**S/S**: similar to meningitis, AMS, personality changes, seizures
Bugs: Viral: echo, coxsackie, mumps, HSV-2 (Mollaret's meningitis aka recurrent aseptic meningitis), adenovirus Bacterial: *by age…* <1m: GBS, E.coli, Listeria 1-23m: S.pneumo, N.mening, H.flu, E.coli 2-50y: N.mening, S.pneumo 50+y: S.pneumo, N.mening, Listeria, GNR	**Bugs**: HSV-1 (#1), arboviruses (Saint Louis Encephalitis, La Crosse Encephalitis, Eastern Equine Encephalitis, Western Equine Encephalitis), West Nile Virus, Legionella, Rabies Immunocompromised: CMV, HHV-6 (transplant recipieints), VZV
Workup: HCT → LP (routine, HSV PCR, t/c crypto/TB/AFB/viral studies). Send BCx (positive about 66% of the time and may be positive when CSF cultures are negative). If patient seen >7 days after onset of symptoms, PCR may be negative and IgM/IgG antibodies may be useful **<u>Do not wait to start for LP to start abx/antivirals!</u>** Lyme meningitis: CSF Lyme ab is diagnostic but test is not sensitive	**Workup**: HCT → if no abscess LP (routine, HSV PCR, t/c viral/toxo) → t/c MRI and EEG <u>Note on HSV PCR</u>: It is highly sensitive (94-98%) and specific (98-100%), usually positive within 24hrs of onset and stays + for 5-7 days after the start of antiviral therapy VZV PCR may be insensitive, so also send VZV IgG/IgM
Treatment: *empirically…* *Viral*: acyclovir for HSV/VZV, otherwise supportive *Bacterial*: <1m cefotax/ceftriax + ampicillin 1-23m cefotax/ceftriax + vanco 2-50y ceftriax + vanco >50y ceftriax + vanco + ampicillin Trauma ceftriax + vanco Post-NSGY cefepime/mero + vanco Immunocomp. Vanco + ampicillin + cefepime Lyme meningitis: ceftriaxone *Fungal*: amphoB + flucytosine + fluconazole *TB*: rifampin+INH+pyrazinamide+ethambutol, +/- streptomycin ("RIPES") * if trauma: use cefepime or meropenem * Dexamethasone 10 mg IV q6h x 4 days was shown to be beneficial in subgroups with <u>pneumococcal</u> meningitis (and non-inferio for Neisseria and H. flu), 1st dose 20 min before abx. NOTE: You should also consider starting acyclovir empirically while determining b/t bacterial meningitis vs. HSV encephalitis.	**Treatment**: *by bug…* HSV/VZV: acyclovir 10 mg/kg IV q8 x 14+d. CMV: ganciclovir or foscarnet Legionella: azithromycin, quinolone, tetracyclines
Prognosis: - aseptic/viral: most improve over 2 weeks - bacterial: 20% mortality (S. pneumo worst)	**Prognosis**: HSV& EEE = 70% die untreated, 25% treated Others = 5-20% mortality rate
Complications: - During acute presentation: seizures, stroke due to infectious vasculitis, venous sinus thrombosis,	**HSV encephalitis:** High risk of having seizures. Emergency of ant-NMDA

-	cerebral edema, abscess formation, hyponatremia Chronically: hearing loss, epilepsy, cognitive impairment, hydrocephalus	encephalitis post HSV recovery

CT prior to LP: recommended if one of the following present: Altered mental status, seizure within 1 week, immunocompromised, focal neurological deficits, disc edema

MENINGITIS/ENCEPHALITIS ABX DOSING

ANTIBIOTIC	STANDARD DOSE	RENAL ADJUSTMENT	DURATION
Ceftriaxone	2g IV q12	None	14 days for Pneumococcus, S. aureus 7 days for Meningococcus, H. flu 28 days for Lyme 10-14 days for Whipple's, then PO abx x1 yr
Vancomycin	15-20mg/kg IV q8	CrCl <50: 15-20mg/kg IV qd	14 days of Pneumococcus, S. aureus
Cefepime	2g IV q8	CrCl 30-60: 2g BID CrCl 11-29: 2g qd CrCl <11: 1g qd	21 days for gram-negative bacilli
Ampicillin	2g IV q4	CrCl 10-50: 2g q6 CrCl <10: 2g q12	21 days for Listeria
Acyclovir (for HSV encephalitis)	10mg/kg q8	CrCl <50	14-21 days for HSV Make sure to pre-hydrate if possible to avoid ARF.

Call the pharmacy for guidance if you ever have any questions!

CSF INTERPRETATION

Elevated CSF WBC	Elevated CSF Protein
Infectious Bacterial/ TB meningitis, syphilitic meningitis, viral meningitis, meningeal cysticercosis, trichinosis, Amebic meningitis (Naegleria fowleri) *Inflammatory* Sarcoidosis, Connective Tissue Diseases-Lupus, Rheumatoid Arthritis, Behcet's, Sjogren's syndrome, MS (<50), NMO *Neoplastic* Carcinomatous meningitis *Medications* Intrathecal chemo, NSAIDS, DMARDS (MTX, IVIG), Bactrim, lamictal, tegretol *Vascular* SAH	Diabetes Age (protein = age per Dr. Price) GBS Demyelinating disease Bacterial meningitis, Neurosyphilis, TB meningitis, trauma, fungal meningitis *Severely elevated (100-500)* TB, bacterial meningitis, Brain tumor, cord tumor/trauma (Spinal block)

Differential Diagnosis for Brainstem Encephalitis		
Infections	*Viruses*	Enteroviruses: Enterovirus A71/D68 bulbar poliomyelitis, coxsackievirus A16, echovirus

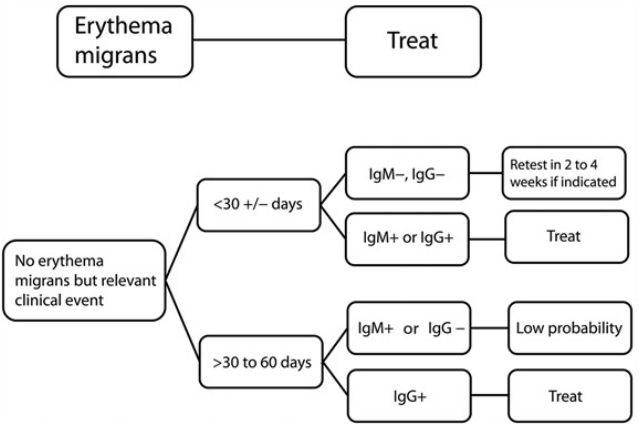
		Herpes: HSV 1&2, HHV 6, EBV, CMV, VZV
		Flaviviruses: W Nile, Japanese encephalitis virus, St. Louis encephalitis virus, Powassan virus
	Other	HIV, Rabies, JC virus
	Bacteria	Listeria**,** TB, syphilis, Lyme Brucella, Salmonella, Nocardia, Legionella
	Fungi/Parasites	Cryptococcus neoformans, Toxoplasma gondii, schistosomiasis
Autoimmune		GBS, Miller Fisher syndrome, Bickerstaff, NMO
		Behcet's, Lupus, Sjogren's syndrome, sarcoid, CLIPPERS
Paraneoplastic Syndromes		anti-Hu and anti-Ma2 antibody-associated encephalitis
Neoplasia		Lymphoma, leptomeningeal metastases, CNS PTLD

BACTERIAL CEREBRAL ABSCESS, EPIDURAL ABSCESS

- Etiologies: direct spread from adjacent compartments (sinuses), open skull trauma, recent neurosurgery or ENT surgery, hematogenous spread from another site of infection (ex. Endocarditis).
- MRI: ring-enhancing lesion with surrounding edema, **central diffusion restriction**
- Diagnostics: Imaging, blood cultures
- Eventually usually requires surgical evacuation (more urgent in the case of epidural abscess, which can cause cord compression).
- For abx, make sure to also cover for anaerobes

LYME DISEASE:

- Etiologies: *Borrelia burgdorferi* transmitted by a tick, tick must stay attached for 24-48 hours to transmit spirochete to host
- Presentation:
    - Systemic: targetoid rash, monoarthritis or oligoarthritis, cardiac abnormalities (heart block)
    - Cranial neuritis: unilateral or b/l 7th nerve palsy most common, but CN 3, 4, 6, and 8 can also be affected. Etiology: mild meningitis
    - Meningitis: most common symptom is headache, with or without meningismus. CSF: lymphocytic pleocytosis, mildly increased protein
    - Radiculoneuritis (electrophysiologically, a mononeuritis multiplex)
    - CNS infection: rare in USA, more common in Europe
- Diagnosis: two-step - (1) ELISA for B. burgdorferi. If negative, patient does not have Lyme disease. If positive, (2) Western blot for IgG and IgM. **Patients with active neuroborreliosis will have a CSF pleocytosis**
- Treatment: previous standard of care was IV antibiotics (ceftriaxone or cefotaxime), although oral doxycyline x 2-4 weeks has also been shown to be effective and endorsed by most recent AAN guidelines



Testing for Lyme disease. From Continuum, August 2021. Use only if ELISA is positive

VIRAL INFECTIONS OF THE CNS:

- HSV: see above
- VZV:
    - Ramsay-Hunt Syndrome: 7th and 8th nerve involvement secondary to VZV reactivation. Often called for stroke evaluation. Check for vesicles in ipsilateral ear.
    - Necrotizing myelopathy: within 1 to 2 weeks after development of a dermatomal rash
    - VZV vasculopathy (affecting large intracranial vessels leading to strokes)
    - Zoster ophthalmicus
    - Necrotizing retinitis/optic neuritis
    - Transverse myelitis
- West Nile Virus: diencephalitis + basal ganglia involvement, LMN in spinal cord (flaccid paralysis) - consider in cases of acute flaccid paralysis with motor neuron-only involvement on EMG
- HHV-6: Consider in patients with RECENT BMT.
    - Clinical presentation: amnestic, progresses to encephalitis with temporal lobe epilepsy, and can also include insomnia, SIADH.
    - Dx by HHV-6 PCR in the CSF, not 100% sensitive, and tx w/ foscarnet

FUNGAL INFECTIONS OF THE BRAIN:

- Mucormycosis: think direct extension from the nasal cavity in patients with recent ENT surgery, poorly controlled diabetes, immunocompromised, hemochromatosis, or IVDU.
    - Angioinvasive, leading to stroke and ICH.
    - Tx: amphotericin and urgent surgical debridement
- Aspergillus: similar risk factors as mucor, most notably immunocompromise.
    - Also at risk of stroke and hemorrhage due to angioinvasion.
    - Tx: voriconazole
- Cryptococcus: meningitis as above, but can also present as a space-occupying lesion. **Commonly causes elevated ICP requiring serial lumbar punctures.** Send cryptococcal antigen in CSF and serum if concerned
- Less common in PA but good to consider: Histoplasmosis, Coccidiomycosis

CNS TUBERCULOSIS:

- Can take a lot of different forms.
- More common in patients with HIV
- Hallmark pathologic feature: thick exudate in basilar cisterns and resultant hydrocephalus, CN III, VII and VIII palsies, also affects II, IV, and VI
- Dx: CSF acid-fast bacillus smear (+ in 5% to 30%) and culture (45% to 90%) – can take weeks
- Tx: First-line rifampin, isoniazid (take B6 to avoid neuropathy), pyrazinamide, ethambutol (RIPE) +/- streptomycin.
- Tuberculous meningitis presents insidiously, then in later stages causes severe basilar meningitis, strokes due to involvement of basilar vessels, and hydrocephalus. It is poorly reversible at this stage.

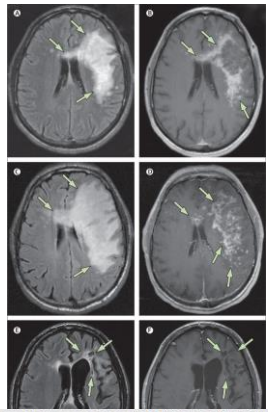
PARASITIC INFECTIONS OF THE BRAIN:

- Toxoplasmosis: immunocompromised (most commonly HIV+ w/ CD4<100)
    - Clinical presentation: often found in the basal ganglia, so can see subacute development of contralateral hemiparesis or movement disorder, confusion
    - Imaging: ring-enhancing lesions w/ edema
    - Tx: sulfadiazine (clinda if sulfa allergy) and pyrimethamine
    - Ddx often also includes primary CNS lymphoma; definitive diagnosis between these two often requires biopsy.
- Neurocysticercosis:
    - #1 cause of acquired epilepsy worldwide; can present many years after infection
    - Clinical presentation: seizures > hydrocephalus
    - Treatment depends on stage of cysts, but if seizures present, should always include antiepileptic.

OTHER NOTABLE CNS INFECTIOUS PROCESSES:

- Infectious CNS Vasculitis:
    - While this can be inflammatory, it can also be secondary to meningitis, HIV, VZV, syphilis, mucor, aspergillus.
    - Can often lead to stroke
    - Resolves w/ treatment of underlying infection

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)



- Caused by reactivation of JC Virus
- Epi: 3-5% risk w/ HIV, 0.1% risk with natalizumab. Risk Factors: HIV/AIDS (85% of cases; CD4<200); on steroids, JCV Ab(+), natalizumab (Tysabri), rituximab, alemtuzumab, brentuximab, fingolamide, dimethyl fumarate
- Dx: MRI brain w/wo GAD traditionally shows large, confluent non-enhancing lesions (occasionally enhance if HIV on treatment or in natalizumab patients); CSF JCV Ab (80% sens/95% spec). Can see advancing rim of DWI around lesion (see photo)
- This is a send-out lab so can take a few days to come back
- Tx: HAART if HIV(+), Plex to remove natalizumab. Consider pembrolizumab. Treatment can lead to immune reconstitution inflammatory syndrome characterized by more prominent enhancement. PRognosis is very poor, better if HIV associated

NEUROSYPHILIS

Manifestations

- Acute meningitis/encephalitis, optic neuritis or retinitis. Encephalitis may be acute or chronic and often involves bilateral mesial temporal lobes, but is a "great mimicker."
- Stroke, due to meningovascular syphilis between 4 and 7 yrs after initial infxn.
- Tabes dorsalis, due to posterior column involvement after 15+ yrs of infxn: Shooting pains due to root involvement, incontinence & progresses to sensory ataxia w/ areflexia.
- Syphilitic paresis, often with rapidly progressive dementia, due to cortical involvement after 15+ yrs of infxn.

TABLE 10-2 Suggested Neurosyphilis Diagnostic Criteria

▶ Asymptomatic Neurosyphilis

Reactive serum treponemal test

AND

Reactive CSF-VDRL

If CSF-VDRL is negative:

Reactive CSF-treponemal test

AND

1. In a patient not infected with HIV: CSF WBCs >5/μL or CSF protein >45 mg/dL
2. In a patient who is HIV infected with peripheral blood CD4+ T cells <200/μL and undetectable plasma HIV RNA and on antiretroviral therapy: CSF WBCs >5/μL
3. In a patient who is HIV infected with peripheral blood CD4+ T cells >200/μL or detectable plasma HIV RNA or not taking antiretroviral medications: reactive CSF-FTA-ABS and CSF WBCs >20/μL

▶ Symptomatic Neurosyphilis[a]

Reactive serum treponemal test

AND

Symptoms and signs of neurosyphilis

AND

Reactive CSF-VDRL

OR

CSF WBCs >5/μL or CSF protein >45 mg/dL

Management

- If RPR is positive: send confirmatory serum Treponemal test (FT-ABS), call state lab (215-685-6737) to report positive test, and confirm if patient was previously treated or requires treatment. At this point, would also include ID team in care.
- Serum treponemal tests remain positive for life. Nontreponemal tests are highest levels during secondary or early latent stage infections. Even without treatment, the antibody levels can decline: 25% of untreated patients' VDRL becomes nonreactive. Titers can be falsely negative very early or very late in the disease
- 10% of elderly individuals age 80 or older have a low titer false-positive VDRL.
- CSF VDRL is specific and not sensitive thus negative CSF VDRL does not rule out neurosyphilis
- Positive CSF VDRL is diagnostic of neurosyphilis (See below)
- In the absence of a reactive CSF VDRL, an elevated CSF WBC and protein concentration and a reactive serum treponemal test are sufficient evidence to treat for neurosyphilis (see below)
- Rx: IV penicillin G for ALL forms of neurosyphilis (3-4 million U IV q4 x 10-14d)

NEURO-HIV

Adapted from Eric Hanauer's "Neurology Survival Guide," University of Rochester School of Medicine.

Summary of neurologic complications of HIV infection is noted below, including opportunistic infections that may occur when CD4 count is low. Treatment of the neurologic complications of

NEURO-ID

HIV is largely HAART + symptomatic management. Treatment for opportunistic infections is treating the underlying infection (many discussed in the previous pages).

Brain (Predominantly Non-focal): AIDs dementia complex (subcortical) Acute HIV encephalitis (seroconversion) CMV encephalitis (CD4 usually <50) VZV or HSV encephalitis Metabolic encephalopathies Depression/pseudodementia **Meninges** Aseptic meningitis (seroconversion) Chronic meningitis (tx-steroids) Cryptococcal meningitis TB meningitis Syphilitic meningitis Lymphomatous meningitis	**Brain (Predominantly Focal)** Toxoplasmosis (CD4 usually <200) Primary CNS lymphoma PML (JC virus) Cryptococcus (CD4<100) *-Hold ARVs with CNS crypto as risk of IRIS* Brain abscess/tuberculoma Neurosyphilis Nonbacterial endocarditis Vasculitis HIV vasculopathy HIV-associated hypercoagulability Cerebral hemorrhage with thrombocytopenia Seizures (from above)
Radiculopathy & Polyneuropathy VZV radiculitis LS polyradiculopathy (late in disease) - Ddx: CMV, lymphoma, diffuse infiltrative lymphomatous syndrome AIDP/CIDP-occurs with seroconversion - CSF pleocytosis (10-50 WBC) Sensory neuronopathy (late in disease) Cranial mononeuropathy (early) Distal symmetric polyneuropathy (late) Mononeuritis multiplex (usually late) -a/w with OI, vasculitis, lymphoma Epidural lipomatosis (from HIV meds)	**Spinal Cord** Vacuolar myelopathy HSV/VZV myelitis Toxoplasmosis myelitis TB Syphilis **Muscle** Polymyositis (any stage) AZT-induced with ragged red fibers Nemaline rod-like myopathy

INFECTIONS OF THE PERIPHERAL NERVOUS SYSTEM

Anterior horn cell: WNV, enterovirus, Japanese encephalitis virus, dengue, tick-born encephalitis. All are acute-onset with associated meningoencephalitis. If chronic, consider HIV or HTLV1

Radiculopathy: Lyme, VZV (also associated with myelitis), HSV-2 (lumbosacral predominance), CMV (lumbosacral in immunocompromised patients), TB (vertebral compression or arachnoiditis of the cauda equina)

Cranial neuropathy: Leprosy, diphtheria (lower cranial nerves), botulism (poor pupillary response), VZV, Lyme disease, cryptococcus, TB, syphilis - 25% of facial nerve palsies are infectious

Mononeuropathy: leprosy (multiplex), hepatitis B and C (multiplex), Lyme disease, HIV, and CMV

Polyneuropathy: hepatitis B (vasculitis esp PAN), hepatitis C (w/ cryoglobulinemia), HIV, HTLV1, leprosy, diptheria (initially bulbar, then diffuse)

- CIDP: HIV, hepatitis B/C, HTLV1 through a parainfectious process
- Autonomic dysfunction: Chagas disease, HIV, HTLV1, leprosy, diptheria, botulism, Lyme

Myopathy: viral infections (i.e. influenza), pyomyositis with bacterial infection in susceptible hosts (HIV, diabetes, malignancy; dx with muscle MRI), trichinosis myositis (think periorbital and facial edema), HIV (opportunistic infections or HAART side effects),, HTLV-1 (associated with myelopathy)

Tetanus:

- Pathogenesis: toxin enters pre-synaptic terminals and impairs inhibitory neurotransmission. Increased risk with lack of vaccination
- Presentation: 2 weeks of symptoms, followed by recovery around 1 month. Characterized by painful, stimulus-induced muscle spasms and rigidity, trimsmus, facial muscle spasm, opisthonus, laryngospasm
- Diagnosis: EMG will show continuous firing in agonist and antagonist muscles (similar to stiff-person syndrome)
- Treatment: administration of tetanus immunoglobulin, treatment of spasms, and intensive supportive care

Botulism:

- Pathogenesis: toxin interferes with SNARE polypeptide complex, preventing fusion of acetylcholine vesicles with presynaptic membrane
- Presentation: (1) infant botulism, (2) foodborne botulism, (3) wound botulism, (4) adult intestinal colonization botulism, and (5) iatrogenic botulism. Sx: constipation, descending muscle weakness (cranial-> caudal), respiratory failure
- Diagnosis: botulism toxin in stool, EMG with presynaptic NMJ defect (increment with 10Hz rep stim, no change with 3Hz rep stim)
- Treatment: botulinum antitoxin

Infectious disease	Clinical clues
Botulism	Cranial nerve dysfunction including pupillary reaction dysfunction, limb weakness, gastrointestinal symptoms
	Presynaptic neuromuscular junction transmission defect on EMG without neurogenic changes
	Food contamination, drug use
Chagas disease	Autonomic dysfunction
	Cardiomyopathy and cardiac arrhythmia
	Megacolon, megaesophagus
	Cardioembolic stroke
	From Latin America
Diphtheria	Acute demyelinating neuropathy with cranial nerve dysfunction followed by limb weakness (biphasic course), accommodation dysfunction, myocarditis
	Preceding pharyngitis, cervical lymphadenopathy
	Lack of vaccination
Hepatitis B virus	Mononeuropathy or mononeuropathy multiplex
	Polyarteritis nodosa
	Elevated liver function tests
	Risk factors: human immunodeficiency virus (HIV) infection, high-risk sexual behavior, IV drug use, lack of vaccination, blood transfusion, hemodialysis, health care worker
Hepatitis C virus	Mononeuropathy or mononeuropathy multiplex; distal axonal neuropathy, may be asymmetric
	Cryoglobulinemia, elevated liver function tests
	Risk factors: IV drug use, HIV infection, blood transfusion, tattoos, high-risk sexual behavior, hemodialysis, health care worker
Leprosy	Rash or other skin lesions associated with numbness
	Enlarged, palpable nerves
	Mononeuropathies, particularly at superficial sites including facial palsy; may appear as compression neuropathies
	Length-dependent sensorimotor neuropathy
	From Brazil, Southeast Asia, Africa, Southern United States or armadillo exposure
Lyme disease	Facial palsy or polyradiculopathy (EMG usually with preganglionic pattern); erythema migrans
	Tick exposure
	Northeast United States
Pyomyositis	Focal muscle pain, edema, fever, especially in quadriceps
	Risk factors: male sex, younger age, IV drug use, diabetes, trauma
Tetanus	Painful muscle spasms and rigidity; trismus, risus sardonicus, opisthotonus
	Recent wound, lack of vaccination, IV drug use
Trichinosis	Fever, gastrointestinal symptoms, periorbital and facial edema
	Ingestion of poorly cooked meat, especially pork
	Eosinophilia
Varicella-zoster virus	Thoracic radiculopathy
	Vesicular rash in dermatomal pattern
	Older or immunosuppressed
West Nile virus	Flaccid paralysis, lack of sensory changes
	Meningoencephalitis
	EMG with preganglionic/motor neuron pattern
	T2 hyperintensities on MRI, especially in anterior horn cells; nerve root enhancement
	Late summer

EMG = electromyography; IV = intravenous; MRI = magnetic resonance imaging.

From Continuum article by Samantha LaRusso, August 2021

NEURO-INFLAMMATORY

MULTIPLE SCLEROSIS

CLINICAL MANIFESTATIONS:

- Sensory symptoms in limbs or face, unilateral visual loss, acute or subacute motor weakness, diplopia, gait disturbance and balance problems, L'hermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck), Uthoff's phenomenon (recurrence/emergence of neuro symptoms with heat), vertigo, bladder problems, limb ataxia, acute transverse myelitis, and pain. Suspect when symptoms develop over **hours to days**, often gradually remit, can be monofocal or multifocal.
- ACCUMULATING OVER TIME: cognitive symptoms, neuropsychiatric symptoms, fatigue.

SUBTYPES OF MS:

- **Relapsing-Remitting MS (RRMS):** clearly defined attacks with full or incomplete recovery, may evolve into **Secondary Progressive MS (SPMS)** after 10-20 years. **SPMS** is characterized by accrual of disability without discrete clinical or radiographic flares
- **Primary Progressive MS (PPMS):** progressive accumulation of disability – 10% of cases, typically older at presentation. Tend to progress faster.
- More rarely:
    - **Marburg variant, tumefactive MS**: tumor-like variant with lesions > 2cm, +/- ring-enhancement, edema, mass effect
    - **Balo's concentric sclerosis:** MRI w/onion-ring like lesions, layered in white matter

DEMOGRAPHIC: Women > Men (3:1 ratio), mean age of onset 25-29 for RRMS and 39-41 for PPMS; but can range peds - 70s rarely; increased in pts with other AI conditions, siblings risk 3-5%, low Vit D suspected.

MAKING THE DIAGNOSIS:

- Radiologically isolated syndrome: Incidentally discovered MS appearing lesion.
    - Manage by imaging entire neuroaxis and can repeat in 6 months then annually for 5 years.
    - 1/3 develop MS in 5 years, higher if lesion is in the spine.
- Clinically isolated syndrome: Monophasic clinical episode with subjective symptoms and objective findings that reflect a demyelinating event.
    - Manage with MRI neuroaxis and LP for bands. Repeat MRI in 6 months then annually for 5 years.
    - 60-80% risk of developing MS, lower risk if MRI negative and LP normal.
- To diagnose MS- **MCDONALD CRITERIA 2017 for Diagnosis of MS- Dissemination** of CNS lesions in space and time.
    - In time: Enhancing and non-enhancing lesions at one time point, ≥2 non-enhancing lesions and different time points, one lesion + CSF bands (if WBC<50, protein<100), or multiple clinical attacks.
    - In space: ≥2 lesions in MS specific area-periventricular, juxtacortical, infratentorial, spinal cord, or clinical attacks at different site (ex. transverse myelitis/optic neuritis)

WORKUP:

Imaging: MRI Brain/C/T spine w/ and w/o contrast on 3T scanner, "MS protocol" (important because different sequences obtained that are useful in tracking changes over time. Also, with this protocol contrast will only be given if a new lesion is seen by radiology).

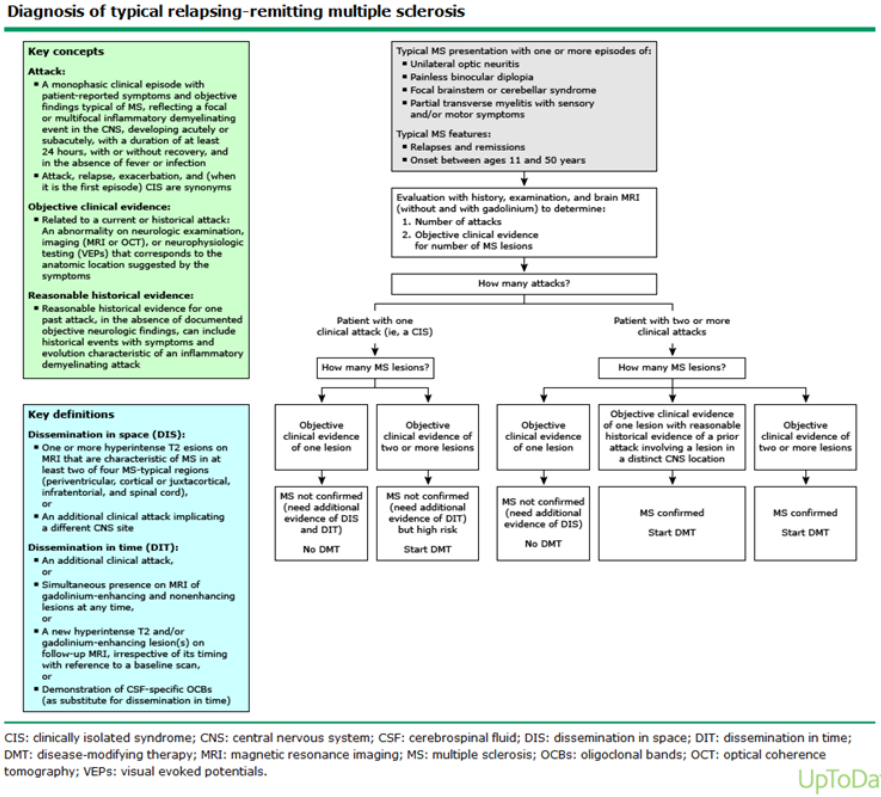
- Look for lesions in 4 typical regions – 1) periventricular -- "Dawson's Fingers" 2) cortical/juxtacortical 3) Infratentorial 4) spinal cord less than 2 vertebral segments (if longer think NMO), dorsolateral cord is most common
- Active lesions will have contrast enhancement (lasts up to 8 weeks), classic pattern is an open ring of enhancement/demyelination
- T1 black holes: Longstanding demyelination and axonal loss chronic lesions

NEURO-INFLAMMATORY

LP: looking for OCBs (found in 95% of pts with MS and 8% of people without MS), NMO, MOG. Protein is usually <100. WBC should be <50 (normal in ⅓, 5-15 in ⅓, and 15-50 in ⅓).
Visual evoked potentials: (abnormal in 50-90%). Outpatient study, can be performed in our clinic.
Optical Coherence Tomography (OCT): measures thickness of retinal nerves, reduced in 85% of people with optic neuritis. Outpatient study, can be performed in our clinic.

Differential Diagnosis:

Autoimmune/ Inflammatory	*Infectious*
SLE	HIV/opportunistic infections
Sarcoidosis	Whipple's Disease
NMO	Lyme
ADEM	PML
Vasculitis	HTLV-1
Vascular	*Metabolic*
Small vessel ischemic disease	B12/Cu deficiency
Spinal cord infarction	Central pontine myelinolysis
Complicated migraine	Leukodystrophies (metabolic and genetic)
Neoplastic	
Primary CNS lymphoma	
Intravascular lymphoma	



CIS: clinically isolated syndrome; CNS: central nervous system; CSF: cerebrospinal fluid; DIS: dissemination in space; DIT: dissemination in time; DMT: disease-modifying therapy; MRI: magnetic resonance imaging; MS: multiple sclerosis; OCBs: oligoclonal bands; OCT: optical coherence tomography; VEPs: visual evoked potentials.

UpToDate®

MS DISEASE MODIFYING THERAPIES (DMT)

Principles of DMT:
You will be starting DMT on patient's who meet McDonald criteria or who have CIS with high risk features (multiple lesions, spinal cord lesion).

- There is a tradeoff between side effect profile and effectiveness. Generally, we are now leaning more towards treating with higher effectiveness agents up front to prevent progression, especially as safety of newer agents has improved.
- Choice of DMT depends on patients preferred route of administration – oral, infusion, injectable – family planning, severity on presentation, and MS subtype.

- For **Primary Progressive MS**, **ocrelizumab** is only approved therapy.
- For **Relapsing Remitting MS**, there are now 22.

RRMS DMT MEDICATION PROFILES

Injectables:

1)Interferons (Avonex, Rebif, Plegridy, Betaseron): The old standard. Low efficacy, subq injectable. First line treatment for mild disease, but there are better options now.

Mechanism: cytokines that modulate immune responsiveness
Risks: hepatotoxicity, and makes people feel crummy

Prelim Screening: CBC, CMP, TSH
Monitoring: yearly CMP, CBC, TSH
Tolerability: lower (can experience flu-like symptoms)

2)Glatiramer acetate (Copaxone): Low efficacy, subq injectable – 3x per week or daily, first line option for mild disease. Safe to conceive with, although generally discontinued after conception.

Mechanism: Mixture of random amino acid polymers similar to myelin basic protein, competes with myelin antigens for T cells
Risks: None
Prelim Screening: None
Monitoring: yearly CBC, CMP as precaution
Tolerability: highest. No medication interactions. Can get lipoatrophy from injections.

3) Ofetumumab (Kesimpta): essentially an injectable version of ocrelizumab (Ocrevus), given in monthly self-injections. See mechanism, risks/screening/monitoring noted below under Ocrevus.

Oral agents:

1)Teriflunamide (Aubagio): Lower efficacy oral daily drug; used mainly for patients >40 who can't tolerate injectables.

Mechanism: active metabolite inhibits pyrimidine biosynthesis and disrupts interaction of T cells with antigen presenting cells
Risks: Category X in pregnancy (metabolites are teratogens for 2 years) in both women and men (found in semen)
Prelim Screening: Quant Gold TB test, CMP, pregnancy test
Monitoring: Monthly LFTs for first 6 months, CBC/CMP every 6 months
Tolerability: lower. More commonly GI upset, hair thinning, paresthesias. More rarely, peripheral neuropathy or SJS.

2)Dimethyl fumarate (Tecfidera): Higher efficacy BID oral agent with minimal monitoring and workup, used for patients with more aggressive disease. Can cause flushing and Gi upset. There is a new version of this medication recently approved called diroximel fumarate (Vumerity), which breaks down to the exact same metabolite/active ingredient, but has fewer GI side effects.

Mechanism: activates pathway involved in cellular response to oxidative stress, unclear why this works in MS
Risks: Rare cases of PML (risk 1/10,000), severe lymphopenia, liver toxicity
Prelim Screening: CBC, CMP to assess LFTs and baseline lymphocyte count, JC virus testing
Monitoring: CBC every 3 months, looking for absolute lymphocyte count < 500. Yearly JC virus testing
Tolerability: can get flushing rxn when starting (rec taking with ASA and a meal), eventually this stops. Can also get GI upset

3)Fingolomid (Gilenya): Highest efficacy daily oral option used for more aggressive disease. Avoid with cardiac and pulmonary comorbidities. Not the best option if patients have trouble staying compliant or making it to lots of doctors appointments.

Mechanism: sphingosine analogue that modules sphingosine-1-phosphate receptor and sequesters lymphocytes in lymph nodes
Risks: prolonged QT, bradycardia (similar receptors present in heart), severe lymphopenia, infections (Crypto meningitis, PML). Avoid if pt has cardiac or pulmonary comorbidities.
Prelim Screening: EKG, further cardiac workup if there is evidence of abnormal conduction, ophtho exam to rule out macular edema, Derm eval due to risk of skin cancer, VZV IgG in serum, CBC, CMP, JC virus, vaccination history
NOTE: first dose is given in doctor's office to observe for bradycardia x 6 hours. If doses missed for 14 days will need to restart this process

NOTE: avoid live attenuated vaccines (MMR/VZV)
Monitoring: Yearly JC virus (PML risk 1/10,000), CMP, CBC every 3 months for hepatoxicity, lymphocyte counts, yearly skin check for skin cancer, OCT after first 3 months then yearly to assess for macular edema
Tolerability: can get headache, GI upset. More rarely, macular edema, crypto, shingles, BCC, liver toxicity, PML

4) **Siponimod** (Mayzent): newer oral medication. Similar to fingolimod except lower risk of lymphopenia and does not require cardiac monitoring.
Mechanism: selective sphingosine-1-phosphate receptor modulator
Risks: liver toxicity and BCC
Prelim Screening: CMP, CBC, JCV, VZV, EKG, OCT, ophtho, derm eval, genetic testing.
Monitoring: See fingolomid section
Tolerability: high. more commonly, can get headache, UTI, hypertension.

5) **Ponesimod** (Ponvory): newest oral medication (came out in 2021). Similar to other S1Ps
Mechanism: sphingosine-1-phosphate receptor modulator
Risks: Most common: elevated LFTs, URIs/increased risk of infection, and HTN. Rarer: cutaneous malignancy, bradycardia or 1st degree heart block, macular edema, liver injury. **C/I** if recent hx of stroke, MI, advanced CHF, certain arrhythmias.
Prelim Screening: EKG, CBC, LFTs, ophtho eval, VZV, derm eval, cardiac eval if prior CV hx.
Monitoring: See fingolomid section (requires first dose cardiac monitoring)
Tolerability: Good. Initial dose must be titrated on a specific regimen (see UpToDate).

6) Cladribine (Mavenclad). Newer medication for MS, also doubles as a chemotherapy agent for hairy cell leukemia. Administered as 2 year course, then do not need to keep giving
Mechanism: purine analog. Thought to work in MS by B cell depletion.
Risks: shingles, alopecia, cancer, PML, lymphopenia
Prelim Screening: CMP, CBC, JCV, VZV, quant gold, hepatitis studies, normal ALC, no cancer.
Monitoring: CBC, LFTs.
Tolerability: medium. more commonly, can get headache, sore throat, cold symptoms, nausea, more serious AEs noted above.

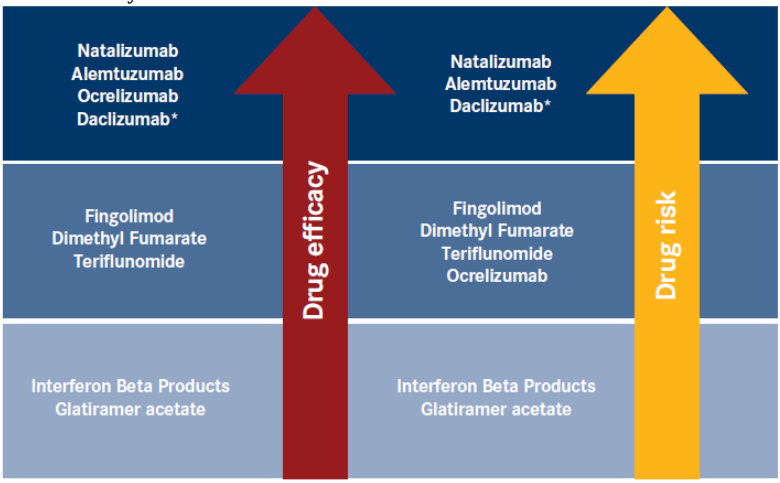
Infusions:

1)Ocrelizumab (Ocrevus): high efficacy infusion (q2 weeks x 1, then q6 months) for aggressive RRMS or PPMS. Also useful for patients who want to become pregnant.
Mechanism: anti-CD20 antibody leading to B-cell depletion (like Rituximab)
Risks: Thus far PML has not been reported. Contraindicated with active Hep B infection. Small increase in risk of malignancy and at increased risk for infections.
Prelim Screening: Quant Gold, VZV IgG in serum, Hepatitis B+C, CBC, CMP, HIV, Quantitative Immunoglobulins, Total B cells, Mammogram for women over 40, immunization history (Live-attenuated vaccines NOT recommended during Ocrevus treatment – MMR/VZV vaccines)
Monitoring: CD19 (want to be low), CBC, CMP a month or two prior to each dose
Tolerability: high. Most common AE is an infusion reactions, most frequently with the first round, improves with subsequent doses.

2)Natalizumab (Tysabri): high efficacy monthly infusion for aggressive RRMS. Carries significant risk of PML (4/1000) so don't use with other impaired immunity. Stop other immunosuppressants 1-3 months prior to decrease PML risk (washout)

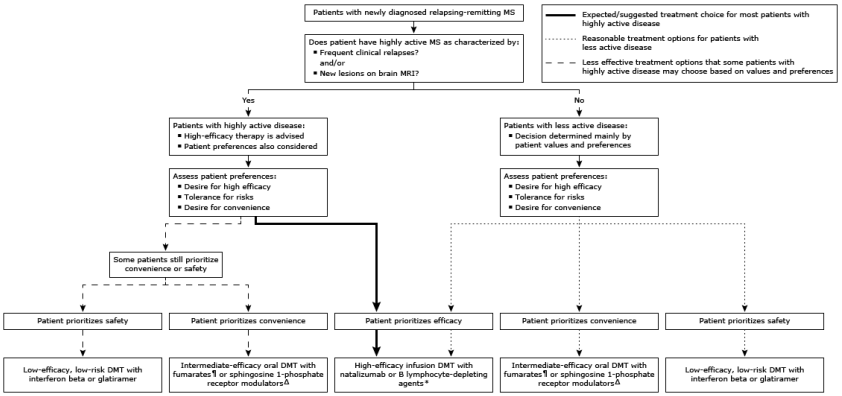
Mechanism: monoclonal antibody against alpha-4 subunit of integrin molecules – limits adhesion and transmigration of leukocytes
Risks: PML – risk highest if + JCV antibody (index >0.9 highest risk), other immunosuppression, and therapy >24 months, Liver injury. Can get rebound disease if you stop this medication without starting a new one immediately.
Prelim Screening: CBC, CBC, JCV
Monitoring: JCV every 3 months if positive (every 6 months if negative), CBC/CMP q6 months – may see mild leukocytosis due to demargination). Need to enroll in special drug screening program
Tolerability: high, most common AE is an infusion reaction.

3)Alemtuzumab (Lemtrada): Highest efficacy, yearly infusion after daily for first 5 days, generally considered last line for aggressive RRMS
Mechanism: depletion of CD52 expressing T cells, B cells, NK cells, monocytes
Risks: infections (herpes), autoimmune disorders (ITP, thyroid autoimmunity)
Prelim Screening: VZV, Quant TB, CBC, CMP, baseline skin exam
Monitoring: monthly CBC, CMP, CD4/CD8, urinalysis TSH, yearly skin exam
Tolerability: low/medium.



FDA indicates Food and Drug Administration.
Figure reprinted with permission from EW Associates, LLC.

NEURO-INFLAMMATORY



From Uptodate "Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults" by Michael Olek

LOGISTICS OF STARTING AN MS DMT:

Our MS Pharmacists are very helpful and sit right across from the resident workroom! They are wonderful resources to ask about any of these meds, to further discuss DMT options and side effects with your patients, and to guide you through the process of starting your patient on a DMT.

Prior authorization:

1) Send prescription to PCAM outpatient pharmacy with e-prescribe

2) PCAM Pharmacy will conduct prior auth review – 1-2 days

3) If pharmacy can't fill it they will notify you & MS pharmacists to send to another pharmacy

For starting infusion therapies

Open a new encounter and find the "Beacon order" tab. Go under the "Non-Oncology plan", click "create new plan" and search "Ocrevus". Select "Ocrevus cycle 1" for initial dosing (300 mg x 2, 14 days apart). Select "Ocrevus cycle 2" for maintenance (600 mg x 6 months). You will need to send the plan to an attending to cosign. Also place an order for consult to infusion service. *In order to make sure that the medication is ordered correctly the best method is to contact the pharmacists. The MS clinic actually has people who fill out these treatment plans to ensure that all the dosing is adequate.*

Symptom Management (non-DMT): many other symptoms accompany MS and warrant evaluation/treatment as below

- Urinary frequency/urgency: Oxybutinin 2.5-5mg 1-3/day, careful with anticholinergic ASE or Botox in the bladder
- Urinary Retention: Alpha-antagonists: prazosin, doxasozin, tamsulosin. Consider referral to urology for surgical intervention
- Neurogenic Bowel: Bowel regimen - laxative, fibers, bulking agents
- Cognitive Impairment: most commonly attention, executive function, memory, and cognitive slowing
- Care to avoid deliriogenic meds. Cholinesterase inhibitors NOT proven to be effective
- Depression: treat based on other comorbidities: Duloxetine/tricyclics (pain), SSRIs (anxiety), etc.

- Fatigue: consider modafinil (100-400mg daily) or armodafinil; others = Ritalin, Adderall, amantadine
- Gait impairment: Dalfampridine (Ampyra): K-channel blocker, increased walking speed in responders(~¼) ; warning: decreases seizure threshold, worsens TACs; do 25-ft walk test prior and yearly as well as CBC/CMP
- Heat intolerance: environmental changes
- Pain: Trigeminal Neuralgia - CBZ, OXC
- Neuropathic pain: gabapentin, pregabalin
- Headaches: see headache section
- Seizures: more common than general population, treat accordingly, care to avoid Ampyra
- Sexual dysfunction: screening for depression
- Sleep disturbances: RLS, pain, insomnia, sleep apnea
  Spasticity: baclofen, tizanidine, Botox
  Speech dysfunction, dysphagia: refer to SLP
- Tremor: cerebellar tremor not responsive to therapy
- Vertigo: differentiate central vs peripheral, treat as needed

NOTE: also screen for vitamin D deficiency – serum goal is 25 (OH) D 60-80. Can start Cholecalciferol 2000-5000 IU/Day

Treatment of MS in pregnancy

When starting DMT always make sure to ask women about their plans in regard to family planning as this may help you counsel them when choosing the right therapy!

Basic principles:

1. MS does not lead to increased infertility, adverse pregnancy outcomes, or adverse neonatal outcomes.
2. Pregnancy is associated with a decrease in MS disease activity.
3. MS relapse rate increases in the postpartum period (~3months) (higher risk with increased pre-pregnancy relapse rate).
4. Pregnancy does not appear to affect long term disability outcomes.

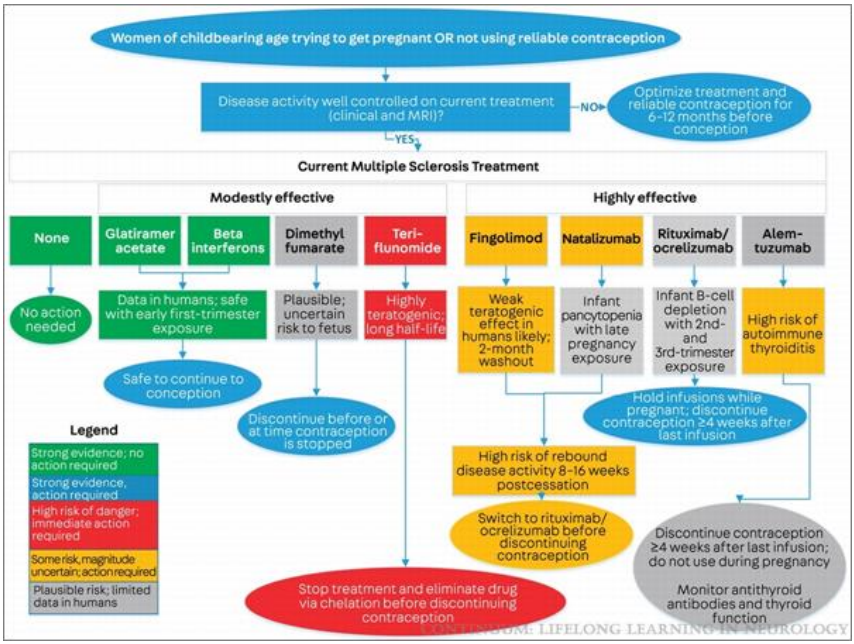
How to counsel women who want to become pregnant: See below diagram.

Scenario 1: Pt who wants to become pregnant in the relatively near future has a new dx RRMS, however with mild disease on imaging (ex. several small supratentorial lesions without spinal cord involvement). Consider starting a modestly effective therapy like Copaxone/Rebif, as accidental first trimester exposure appears safe.

- **If she becomes pregnant, y**ou can likely stop the Copaxone. No DMT has been shown to be completely safe in pregnancy, and the protective effect of pregnancy is probably better than the Copaxone anyway for a patient with mild disease.

Scenario 2: Similar to above, but the patient has more aggressive disease (ex. on Copaxone, but has been accruing lesions, including a symptomatic spinal cord lesion, and on her diagnostic LP she had 9 bands).
Answer: She warrants a more aggressive treatment. Ocrevus would be a good option, as she could start with the loading infusions and then conceive after waiting 3 months. She will therefore be protected as she tries to conceive, and if she becomes pregnant will then accrue the protective benefits of pregnancy.

Scenario 2A: The woman from scenario 2 presents to your clinic already on Fingolimod. She wants to become pregnant. How do you help her achieve this safely?
Answer: Start Ocrevus to reduce the risk of rebound activity before stopping the Fingolimod, then proceed as above.



From Annette Langer-Gould. "Pregnancy and Family Planning in Multiple Sclerosis." Continuum 2019

How to counsel women who have just delivered:

Question: Can my patient breastfeed after delivery?
Answer: Yes! Exclusive breastfeeding reduces risk of postpartum disease activity. Most MS medications are now thought to be safe with breastfeeding. For patients with mild disease, copaxone and interferon beta are compatible with lactation, but given that these are used in patients with mild disease you really won't need to restart them until 6-12 months postpartum. For patients with more active disease, the monoclonal antibodies (like Ocrevus) are unlikely to be passed into breast milk and make it into circulation in the baby. NOTE that fingolimod and dimethyl fumarate are NOT SAFE in lactation.

Question: How to I treat relapses during pregnancy and breastfeeding?
Answer: Short courses of methylpred are safe, but should be reserved for clinically significant relapses and are generally avoided in the first trimester. When used during breastfeeding the patient can pump and dump and should wait 3 hours before nursing after steroid infusion. For steroid refractory relapses use PLEX.

Question: Can I do an MRI with gadolinium during pregnancy and breastfeeding?
Answer: Generally, do not get MRI scans during pregnancy, as plan is unlikely to be altered by MRI findings. Gadolinium is contraindicated during pregnancy and can increase risk of stillbirth and neonatal death. During the postpartum period MRI scans should be obtained in high-risk patients (aggressive disease, active during pregnancy). You can probably forgo the Gad, but if you do think you need to give this, the patient will need to pump for to cover at least 24 hours.

IN THE ED/Acute Presentation:

NEURO-INFLAMMATORY

EXACERBATION PRESENTATION: New symptoms referable to newly active lesions. Expect both vague and specific complaints. Consider: vision loss with painful eye movements (optic neuritis), trigeminal neuralgia, focal weakness, focal numbness, ataxia, paresthesias, incontinence, falls, fatigue.

MANAGEMENT

- **Rule out infection** with UA/UCx & CXR if indicated. If positive, may represent a "**pseudoflare**" - treat the infection first and see if symptoms resolve. Patient may warrant admission to medical service. Steroids are not warranted in this scenario.
    - Pseudoflares are typically worsening of previous symptoms or development of symptoms of prior flares that have resolved. Always ask if symptoms are the same as the patient has had before. Pseudoflares are more common than true MS flares.
- **Rule out Uhtoff's phenomenon** (unmasking of old flare symptoms due to increased body temperature) – similar to a pseudoflare, this would not warrant acute steroid administration.
- **Consider admission** based on following criteria – "can't see" (optic neuritis), "can't pee" (myelitis, neurogenic bladder), "can't eat/swallow," "can't walk," or "can't take care of family." If not admitted, can arrange home IV steroids for the next day via Penn Home Infusions. *Should also admit for first-time receiving IV steroids to monitor for paradoxical (psychiatric) reaction.*
- **Obtain neuroimaging (MRI Brain/C/T spine with and without contrast)** to confirm new contrast-enhancing lesion (only acute/enhancing lesions will respond to steroid burst). If only old lesions present, not likely to improve with steroids. Consider PT/OT evaluation.
- **Start IV Solumedrol** 1 g/d x 3-5 days, not typically followed by pred taper.
- **Order PT/OT/Rehab** service consults immediately if patient is unable to care for self at home on admission.
- **Continue outpatient symptomatic medications**, such as muscle relaxants, SSRIs, stimulants, anticonvulsants, antipsychotics, amantadine, etc. Immunomodulating therapies (interferons, glatiramer acetate) can be continued using home supply.

EVIDENCE FOR TREATING MS FLARES IS POOR.

- IV steroids *may* expedite the timing of recovery from a flare
- IV steroids *will not* increase the degree of recovery or the course of disease
- High-dose oral steroids may also expedite recovery, but IV treatment remains standard
- Consider plasma exchange in patients who fail to improve after 5 days of high dose methylprednisolone

Expect 1-2 flares in untreated RRMS patient per year (75% will have at least 1 flare)

Management of MS flares without admitting a known outpatient

Not every patient with an MS flare needs to be sent to the hospital when they develop symptoms concerning for a flare. General rules to follow – if a patient can't walk, can't see, can't pee then they will definitely need to be admitted. If they are dealing with mild symptoms (i.e. sensory) but are otherwise functional then they can be treated with a course of IV steroids at home. Note that obtaining an urgent MRI scan in the ED won't change management here.

-Order a "Consult to Penn Home Infusion"

Primary Reason: MS flare
Access care: provide line per protocol
Current access: peripheral
Medications to infuse: Methylprednisolone 1000 mg IV daily for 3-5 days (provide dates)
Has the patient received this medication before? If no, then order an anaphylaxis kit.
Physician to follow patient: enter your name

-Order the steroids

In the order bar, enter methylprednisolone and expand the search to Database

Select methylprednisolone sodium succ 1000 mg injection SOLR
In the order, fill out 1000mg daily x 3-5 days. **E-fax the prescription to Penn Home Infusion**

-Order GI prophylaxis. Up to you, but typical approach would be omeprazole 40 mg in the morning with supply just for the days you are giving steroids. MAKE SURE you change back to patient's home pharmacy when ordering this med
-You will receive confirmation in your inbox when Penn Home Infusion establishes contact with the patient.

OPTIC NEURITIS

EPIDEMIOLOGY
- Usually 20s-40s, 2:1 F:M
- Expect referrals to the ED by Scheie Eye residents/fellows

NEUROLOGIC FEATURES
- Acute/subacute monocular vision loss/scotoma, red desaturation, painful eye movements (90%)
- Uthoff's phenomenon
- Central vision loss
- +APD
- Fundoscopic exam is normal 2/3 of the time, papilledema in 1/3 of cases

MANAGEMENT
- MRI to evaluate for lesions suspicious for MS
- Consider formal VF testing (Goldmann or Humphrey)—to be done as an outpatient
- Serum AQP4 IgG, ACE, & other tests pending pretest probability for alternative dx
- Admit for IV solumedrol 1g qd x3-5 days (expect delayed recovery after 2-3 weeks)
- Consider initiation of immunomodulatory therapy if patient meets McDonald criteria for MS, however this is often done as an outpatient in follow-up.

Evidence for Steroids in treating Acute Optic Neuritis (*Optic Neuritis Treatment Trial 1992, 1993, 1997*)
· IV steroids - speed vision recovery, no change in acuity vs. placebo at 5 yrs
· IV steroids - 50% less develop clinically definite MS at 2 yrs (8% vs 17%), but no difference at 5 years
- ALWAYS use IV steroids, not oral steroids: increased recurrent ON vs PO/placebo (41% vs 25%) over 5 yrs.
- Newer, smaller trials have demonstrated that bioequivalent doses of PO steroids (i.e. prednisone 1250mg daily) may have similar efficacy as IV steroids, so could consider this on a case-by-case basis

OTHER DEMYELINATING SYNDROMES

NEUROMYELITIS OPTICA Spectrum Disorders

Overview: Inflammatory demyelinating disease w/ episodes of optic neuritis, transverse myelitis, and other symptoms that can mimic MS.
- Epi: 1-4:100k in the US
- Higher female predominance than seen in MS (9:1 F:M ratio (only 2:1 F:M in MS))
- 80% will have + serum aquaporin 4 antibody (water channel protein), meaning 10-20% will be AQP4(-) NMO

  - AQP4(-) NMO): 2:1 F:M, younger age at onset (32 vs. 44 yrs), more likely to involve conus (75% vs. 17%), less likely to relapse than AQP4 Ab (+) pts
- The other 20% may have antibody to MOG (myelin oligodendrocyte glycoprotein)
- High association with other autoimmune disorders (Sjogren's, SLE, MG, celiac, sarcoid), 20-30% of attacks preceded by infxn or vaccination
- generally poor prognosis, <u>should treat aggressively</u>

Making the diagnosis: NMOSD will enter the DDX with many MS patients or patients presenting with isolated ON or transverse myelitis. In several circumstances you can be confident that you are dealing with NMOSD. To make the diagnosis:

- 1 core clinical criteria + positive serology (Serology sent from SERUM not CSF – AQP4 ab 91%sensitive, 100% specific). Ensure it is a cell-based assay
- 2 core clinical criteria (1 of which is longitudinally-extensive transverse myelitis (LETM), ON, area postrema syndrome) with 1 or more clinical attacks and classic MRI findings (negative serology)

<u>Core clinical criteria</u>: LETM, ON, area postrema syndrome, brainstem syndrome, narcolepsy, diencephalic clinical syndrome

<u>MRI findings</u>: optic neuritis with more than ½ of optic nerve or chiasm affected, LETM >3 levels, brainstem lesions

How to distinguish from MS: +AQP4/MOG serum serologies, OCBs less common in CSF, will disappear later in course, LP may have >50 WBC.

MOG+ more likely to have optic nerve involvement, bilateral optic neuritis, monophasic, fewer supratentorial lesions, may include ADEM presentation

<u>Treatment:</u>

Flares: solumedrol and PLEX – start PLEX early if severe/no improvement with steroids. NOTE that IVIG does not have evidence of efficacy for NMO (used in MOG, at least in peds populations) so go straight to PLEX.

DMTs: Start DMARD on all Ab+ patients as high risk of relapse

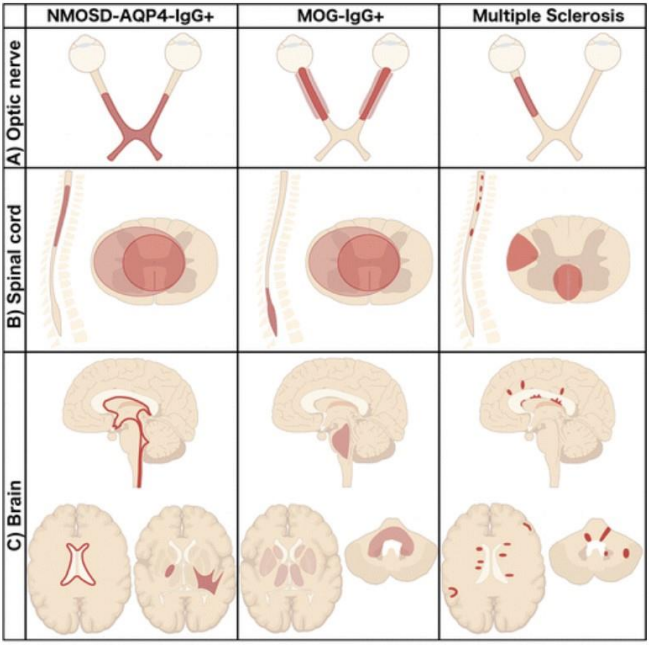
<u>- Eculizumab:</u> has risen as a favorite therapy for NMO. Administered as four weekly doses then maintenance every 2 weeks. Associated with increased risk of Neisseria meningitis, requiring vaccinations and period of prophylaxis.

Mechanism: ab that binds complement C5 and inhibits membrane attack complex
Risks: Neisseria Meningitis
Prelim Screening: CBC, CMP
Monitoring: CBC, CMP

-Can also use Rituxan, azathioprine, mycophenolate (for good review see the 2019 NMO article in MS/inflammatory disease issue of Continuum)

Prognosis: poorer than MS, better if anti-MOG(+), ON less likely to recover in cases of NMO than MS

NEURO-INFLAMMATORY



From “Neuromyelitis Optica Spectrum Disorders: Spectrum of MR Imaging Findings and Their Differential Diagnosis” by Dutra et al.

Clinical Features Differentiating MS, NMO, and MOG

Attribute	Multiple Sclerosis	AQP4-IgG	MOG-IgG
Antecedent infection/ immunization	Rare	Rare	Common
Ages affected	Any (median age at onset in third decade)	Any (median age at onset in fourth decade)	Any (children and young adults more predisposed)
Sex (female: male)	2:1	9:1	1.5:1
Epidemiology	Prevalence: common Ethnicity: whites more predisposed Geographic: regions farthest from equator	Prevalence: rare Ethnicity: African-Americans, Afro-Caribbeans more predisposed Geographic: higher proportion of total demyelinating disease is AQP4-IgG–positive neuromyelitis optica spectrum disorder (NMOSD) in regions where multiple sclerosis prevalence is low	Prevalence: unknown Ethnicity: unknown Geographic: unknown
Most common manifestations	Myelitis, optic neuritis, brainstem, cerebral episodes; myelopathy for progressive multiple sclerosis	NMOSD (any combination of single/recurrent myelitis, optic neuritis, area postrema syndrome)	Initial episode: optic neuritis, acute disseminated encephalomyelitis (ADEM), NMOSD, myelitis Relapse: optic neuritis
Course	Relapsing-remitting from onset in 85% (most later develop secondary progression); 10–15% progressive from onset	Typically relapsing; usually no secondary progression	Monophasic or relapsing; no reports of secondary progression
Attack severity	Usually mild to moderate	Usually moderate to severe	Usually moderate to severe
Recovery from attacks	Good	Often incomplete	Good
CSF	White blood cell count <50/mm^3 (lymphocytic) or can be normal; oligoclonal bands in 85%	White blood cell count variable (usually lymphocytic but can be neutrophilic or eosinophilic); oligoclonal bands in 30%	White blood cell count variable (lymphocytic); oligoclonal bands in <15%
Blood biomarker	NA	AQP4-IgG	MOG-IgG
Brain MRI	Ovoid periventricular, Dawson fingers, juxtacortical, cortical, infratentorial peripheral, ring-/open ring-enhancing	Often normal/nonspecific; if present, area postrema, peri-third/fourth ventricle, splenium, diffuse corpus callosum, pencil-thin ependymal or cloud enhancement	ADEM-like fluffy white matter, deep gray matter, diffuse/confluent brainstem including cerebellar peduncles
Optic nerve MRI	Unilateral; enhancement of <50% of nerve affected; middle of optic nerve	Bilateral; enhancement of >50% of optic nerve; posterior optic pathway involving chiasm	Bilateral; enhancement of >50% of optic nerve; anterior optic pathway (hence optic disc edema common)
Spine MRI	Multiple lesions; short lesions; periphery of cord (dorsal/lateral column); ring or variable enhancement	Single lesion (longitudinally extensive transverse myelitis 85%; short 15%); central on axial; ring or variable enhancement	Multiple lesions; (75% longitudinally extensive transverse myelitis; 25% short); conus involved; central on axial; enhancement variable
Acute treatment	IV steroids; plasma exchange (rarely required)	IV steroids; plasma exchange (often required)	IV steroids; plasma exchange (often required); IVIg (used in children)
Maintenance treatment	Variety of approved immunomodulatory medications	None approved; steroid sparing recommended: azathioprine, mycophenolate mofetil, rituximab, eculizumab, tocilizumab, methotrexate	None approved; none needed if monophasic; steroid sparing for relapsing disease (azathioprine, IVIg, mycophenolate mofetil, methotrexate, rituximab)
Prognosis	Majority ambulatory after 20 years; most disability occurs in secondary progressive phase	Attack-related accumulation of disability; secondary progression rarely if ever occurs	Most disability with first attack; transient seropositivity predicts monophasic course; persistent seropositivity and high titer predict relapsing disease

AQP4 = aquaporin-4; CSF = cerebrospinal fluid; IgG = immunoglobulin G; IV = intravenous; IVIg = intravenous immunoglobulin; MOG = myelin oligodendrocyte glycoprotein; MRI = magnetic resonance imaging; NA = not applicable.

From Eion Flanagan. "Neuromyelitis Optica Spectrum Disorder…" Continuum June 2019

NEURO-INFLAMMATORY

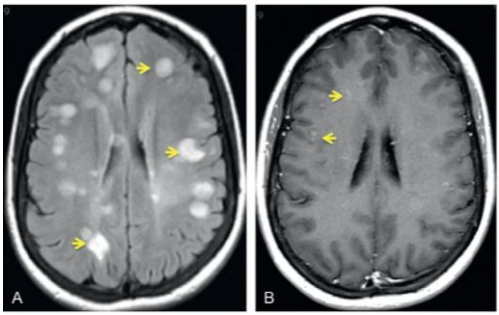
ACUTE DISSEMINATED ENCEPHALOMYELITIS

- Epi: Most common in ages 5-8 (0.4/100k per yr.), rarely in adults
- Risk Factors: Recent infxn or vaccination in 75% of cases (50% of adults), but you're more likely to DIE of flu than suffer ADEM, and you have a 1:1000 chance of getting it if you have the Measles.
- Dx: Image neuroaxis; LP for OCBs, MBP; treat prior/underlying infxn
- *How to distinguish from MS*: ADEM presents with multiple acute lesions (MS typically 1 initial lesion), occurs more often in younger patients, typically monophasic (no new symptoms or lesions after 90 days) (<5% risk of recurrence), lower likelihood of OCBs than MS, no other autoimmune diseases
- Tx: 5 days of high-dose solumedrol PLEX if refractory
- Prognosis: Full recovery in 70-90% of patients, 5% r/o mortality

Differential diagnosis of acute disseminated encephalomyelitis (ADEM)

Vascular	Strokes, CADASIL, amyloid angiopathy, PRES, eclampsia
Infectious	Viral or bacterial encephalitis, HIV encephalopathy, PML, abscess
Toxic	Inhaled heroin, carbon monoxide
Autoimmune	Multiple sclerosis, neurosarcoidosis, Behçet's disease, primary CNS angiitis, vasculitis due to connective tissue diseases such as lupus and Sjögren's disease
Metabolic	Mitochondrial diseases (MELAS, Leber's hereditary optic neuropathy), adrenoleukodystrophy, central and extrapontine myelinolysis
Iatrogenic	Methotrexate, tacrolimus, cyclosporine
Neoplastic	Neoplasms, metastasis, and paraneoplastic syndromes

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; HIV, human immunodeficiency virus; PML, progressive multifocal leukoencephalopathy; CNS, central nervous system; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.



ISOLATED TRANSVERSE MYELITIS

- Epi: 2-8 cases per million, bimodal peak (10-19 yrs, 30-39 yrs)
- Risk Factors: Similar to MS & ADEM, prior autoimmune disease; 15-30% cases are idiopathic
- Dx: (1) bilateral sensorimotor & autonomic cord dysfunction, (2) sensory level, (3) progression between 4hrs and 21days from onset, (4) MRI or CSF pleocytosis or IgG index, (5) exclusion of other diseases
- *How to distinguish from MS*: no intracranial lesions, normal visual evoked potentials, absent OCBs
- Tx: 5 days of solumedrol oral taper; PLEX if refractory
- Prognosis: 50-70% have partial or complete recovery; "Spinal shock" (hypotonia, areflexia, severe weakness) confers poorest prognosis

NEURO-INFLAMMATORY
NEUROSARCOIDOSIS

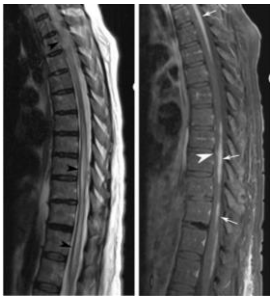
OVERVIEW and EPIDEMIOLOGY
- Most common systemic manifestations of sarcoidosis involve pulmonary, lymph node, ocular, & skin lesions
- Often diagnosed in ages 20-40, F>M
- 5-25% involves the nervous system, while 10-15% is isolated to the CNS (F>M)
- 2/3 of patients will have monophasic illness.

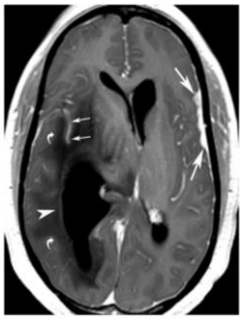
- Neurologic manifestations vary widely
  - Subacute aseptic meningitis
  - Cranial neuropathies are common (VII in ~50% of cases > II in 35% of neuroimaging > VIII > others), and often they are multiple or bilateral
  - Mononeuritis, mononeuritis multiplex, or peripheral sensorimotor polyneuropathy
  - Seizures, encephalopathy, HPA axis dysfunction

DIAGNOSTIC TESTING
- Diagnosis confirmed using Zajicek criteria
  - *Definite*: CNS/PNS biopsy-proven neurosarcoid w/ neurologic symptoms
  - *Probable*: Evidence of neurologic inflammation with histologic evidence of systemic sarcoidosis
  - *Possible*: Presentation of neurologic disease is typical of neurosarcoidosis, but other causes have not been excluded & a tissue diagnosis has not been confirmed

Studies to send:
- Serum ACE 60% sensitive (non-specific), CSF ACE less reliable (25-50% sensitive, <u>false positives observed in malignancy</u>)
- Serum soluble IL-2 receptor is decent – around 80% sensitivity/specificity – performs a bit better than ACE levels
- CSF profile terribly low yield, but often important to exclude other diagnoses
  - Supportive findings include a moderate mononuclear pleocytosis, normal/mild elevation in protein, and rarely you will see hypoglycorrhachia, bands, and elevated IgG index
- Chest imaging to look for hilar lymphadenopathy – CT chest w/ contrast and can tack on abdomen/pelvis too look for lymphadenopathy
  - Here you are looking for non-CNS tissue to biopsy – pulmonary lymph node (EBUS with >80% sensitivity). Skin lesions are also decent (60% sensitivity).
- MRI neuroaxis with and without contrast
  - Characteristic brain findings include lepto- or pachymeningeal (sometimes nodular, often basal) enhancement (40%), subcortical/periventricular WM lesions (mostly along Virchow-Robin spaces, 45% of cases), hydrocephalus (10%)
  - Singular or multiple intraparenchymal lesions may be mistaken for low grade gliomas, abscesses, or demyelinating lesions
  - Cord findings include extradural or intramedullary (25%) longitudinally extensive lesions
- Leptomeningeal/brain bx should be a last resort

NEURO-INFLAMMATORY





DIFFERENTIAL DIAGNOSIS

Cranial neuropathies	Leptomeningeal disease	Parenchymal brain disease
Lyme disease	Tuberculosis	Multiple sclerosis
Multiple sclerosis	Cryptococcal meningitis	CNS Lymphoma
Neuromyelitis optica	Lyme disease	Gliomas
Neurosyphilis	HIV	Craniopharyngioma
HIV	Leptomeningeal metastasis	Germ cell tumors
Varicella zoster virus	Vogt-Koyanagi-Harada disease	Primary CNS angiitis
Optic nerve gliomas	Brucellosis	Lymphocytic hypophysitis
Optic nerve meningiomas	Behçet's disease	Toxoplasmosis
Sjögren's syndrome		Whipple's disease
Systemic lupus erythematosus	**Pachymeningeal disease**	Behçet's disease
Infiltrative neoplasm	ANCA-associated vasculitis	
Lymphoma	IgG4 related pachymeningitis	**Myelopathy**
	Meningiomas	Multiple sclerosis
Neuropathy	Idiopathic pachymeningitis	Neuromyelitis optica
Vasculitic neuropathies	Rosai-Dorfman disease	Degenerative disc disease
Guillain-Barré syndrome	Dural metastasis	Tuberculosis myelitis
Gluten-related disorders	Lymphoma	VZV myelitis
Fibromyalgia	Intracranial hypotension	HTLV-1 associated myelopathy
		Sjögren's syndrome
		Systemic lupus erythematosus
		CMV myeloradiculitis
		Schistosomal myeloradiculopathy

Abbreviations: ANCA, antineutrophilic cytoplasmic antibodies; CNS, central nervous system; CMV, cytomegalovirus; HIV, human immunodeficiency virus; VZV, varicella zoster virus.

TREATMENT

- 3-5 days of 1g IV solumedrol for flares, and patients will often need a slow taper of oral pred – many months to years – depends somewhat on type of neurosarcoidosis (see "Neurologic Sarcoidosis" in UpToDate).
- Consider other acute interventions when indicated (e.g., EVD for obstructive hydrocephalus)
- After presentation and initiation of a steroid taper, wean of steroids should be done slowly. Generally, can allow patient to stabilize for 4 weeks, then can decrease by 5 mg per dose every 2 weeks as tolerated. Exacerbations are most common at 10 mg/day, so when doses are near this level decrease more cautiously.
- If disease recurs, then double prednisone dose.
- Frequently assess with MRI scans as you wean steroids
- TNF alpha antagonist, infliximab, is commonly used in pulmonary sarcoid and may produce a more rapid response compared to other immunomodulators
- Also consider rituximab, azathioprine, MTX, cyclophosphamide, and mycophenolate mofetil
- 70% of patients achieve remission w/ treatment

NEUROMUSCULAR

Peripheral Neuroanatomy

MOVEMENT	ROOT	NERVE	MUSCLE
		Upper Limb	
Shoulder abduction	C5	Suprascapular Axillary Accessory	Supraspinatus (1-15 degrees) Deltoid (15-120 degrees) Trapezius (beyond 120 degrees)
Shoulder ext. rotation	C5/6	Suprascapular	Infraspinatus
Shoulder internal rotation	C5/6	Subscapular	Teres major and subscapularis
Scapular fixation (*winged scapula)	C5/6/7	Long Thoracic	Serratus anterior
Elbow flexion	C5/C6 C5/C6	Musculocutaneous Radial	Biceps (test w/ arm supinated) Brachioradialis (test w/ arm half-pronated and flexed)
Elbow extension	C7	Radial	Triceps
Forearm Supination	C6/7 C5/6	Radial Musculocutaneous	Supinator Biceps
Forearm Pronation	C6/7	Median	Pronator Teres
Wrist extension	C6	Radial	Extensor carpi radialis longus
Finger extension	C7	Posterior interosseous branch of radial	Extensor digitorum communis
Finger flexion	C8	Anterior interosseous branch of median Ulnar	Flexor pollicis longus + flexor digitorum profundus (index) Flexor digitorum profundus (ring +little)
Finger abduction Thumb abduction	T1	Ulnar Median	Dorsal Interossei Abductor pollicis brevis
		Lower limb	
Hip flexion	L2-3	Femoral	Iliopsoas
Hip aDDuction	L2/3/4	Obturator	Adductors
Hip aBDuction	**L5**/S1	Superior gluteal	Gluteus medius Tensor Fascia Latae
Hip extension	S1	Inferior gluteal	Gluteus maximus
Knee flexion	S1	Sciatic	Hamstrings
Knee extension	L3/4	Femoral	Quadriceps
Ankle dorsiflexion	L4/L5	Deep peroneal	Tibialis anterior
Ankle eversion	**L5**	Superficial peroneal	Peroneus longus
Ankle Inversion	**L5**	Tibial	Tibialis posterior
Ankle plantar flexion	S1	Tibial	Gastrocnemius, soleus

NEUROMUSCULAR

ROOT	WEAKNESS/ REFLEX CHANGE	PAIN	NUMBNESS
C3-4	Diaphragm (!) NO reflex	Paraspinal muscles, superior shoulder	Neck
C5	Deltoid, supraspinatus, infraspinatus, rhomboid, biceps, BR - bicep/BR reflexes	Neck/shoulder/anterior arm	Lateral anterior arm and forearm
C6	Deltoid, supraspinatus, infraspinatus, biceps, BR, pronator teres, flexor carpi radialis, extensor carpi radialis - bicep/ BR reflexes	Neck/shoulder anterior upper arm to antecubital fossa	Lateral posterior arm and forearm, thenar eminence, thumb, index finger
C7	Triceps, latissimus, pronator teres, flexor carpi radialis, extensor carpi radialis, extensor digitorum communis - triceps reflex	Neck, shoulder, dorsal forearm	Posterior arm and forearm, middle finger
C8	Extensor indicis proprius, extensor digitorum communis, flexor carpi ulnaris, flexor digitorum profundus, first dorsal interosseous, abductor digiti minimi, abductor pollicis brevis finger flexor reflexes	Neck, shoulder, ulnar forearm	Medial posterior arm and forearm, hypothenar eminence ring and small fingers
T1	flexor carpi ulnaris, flexor digitorum profundus, first dorsal interosseous, abductor digiti minimi, abductor pollicis brevis NO reflex	Neck, shoulder, ulnar arm	Medial anterior arm and forearm
L3	Adductors, quads - decreased knee jerk	Anterior thigh/groin	Anterior and medial thigh
L4	Quads, adductors - decreased knee jerk	Anterior thigh	Lateral thigh and medial calf, great toe
L5	Tibialis anterior, tibialis posterior, EHL, peroneus longus, gluteus medius, tensor fascia latae NO reflex	Posterolateral thigh and calf, down to great toe and dorsal foot	Lateral calf, dorsum of foot,
S1	Gastrocnemius, hamstrings, gluteus maximus -ankle jerk	Posterolateral thigh and calf, extending to heel and lateral toes	Posterior calf, lateral foot, sole of foot

NEUROMUSCULAR

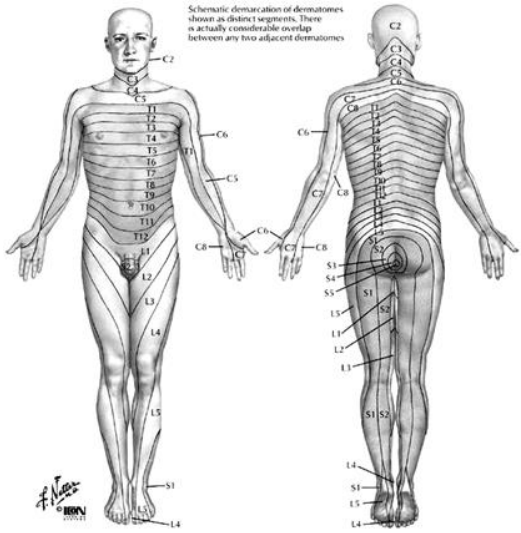
ROOT vs. NERVE LESIONS

	BOTH	**ROOT ONLY**	**NERVE ONLY**
C7 vs. radial	weakness in triceps & wrist ext, loss of triceps reflex	pronation weakness, palmar middle finger sensory loss	weakness of brachioradialis, thumb and index finger sensory changes *radial neuropathies at the spiral groove occur distal to triceps and spare it*
C8/T1 vs. median	weakness of thumb abduction	weakness of finger abduction and extension, sensory loss on small finger and medial forearm	sensory loss confined to thumb, index, and middle fingers
C8/T1 vs. ulnar	weakness of finger abduction, sensory loss in small finger	weakness of thumb abduction and finger extension, sensory loss on medial forearm	
L5 vs. common peroneal	Weakness of foot dorsiflexion and eversion, and big toe extension, sensory loss on lateral calf dorsal foot	weakness of foot inversion and hip aBDuction	

DERMATOMES

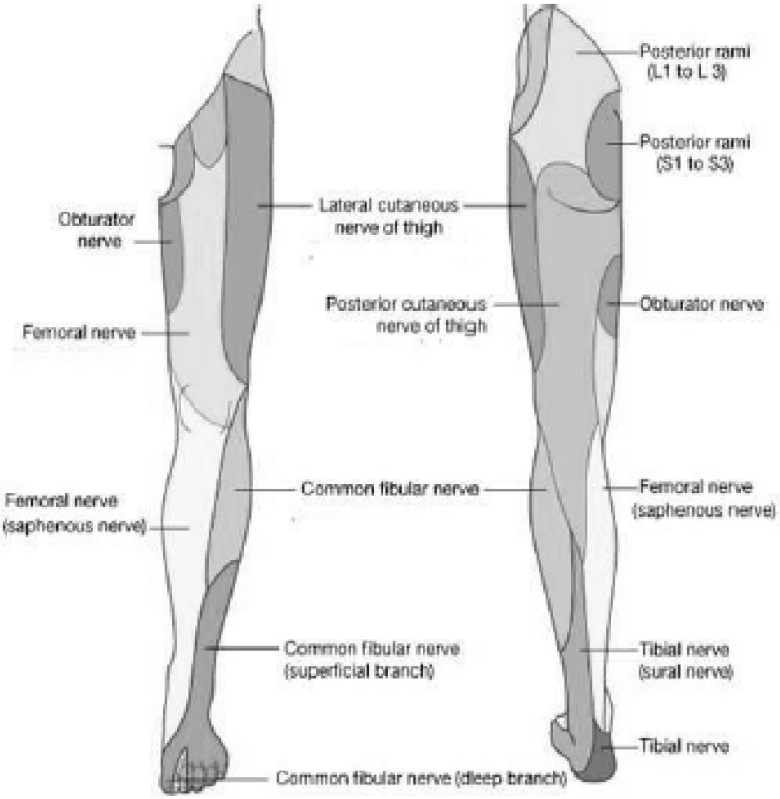
NEUROMUSCULAR

- Substantial variability exists between patients
- When assessing for sensory level, check front and back (conversion/malingering are inconsistent)



Levels of principal dermatomes

C5	Clavicles
C5, 6, 7	Lateral parts of upper limbs
C8, T1	Medial sides of upper limbs
C6	Thumb
C6, 7, 8	Hand
C8	Ring and little fingers
T4	Level of nipples
T10	Level of umbilicus
T12	Inguinal or groin regions
L1, 2, 3, 4	Anterior and inner surfaces of lower limbs
L4, 5, S1	Foot
L4	Medial side of great toe
S1, 2, L5	Posterior and outer surfaces of lower limbs
S1	Lateral margin of foot and little toe
S2, 3, 4	Perineum



Guide to EMG/NCS

Nerve conduction study definitions

SNAP (sensory nerve action potential) amplitude: summated voltage response (in microvolts) of sensory axons

- SNAP amplitudes are often the first element affected in any peripheral nerve process distal to the dorsal root ganglion (plexus and nerves).
- SNAP amplitudes are normal in nerve root lesions proximal to dorsal root ganglion (radiculopathies)
- **Amplitude** reflects axon, **Velocity or peak latency** reflects axon size and myelination.
- Sensory Conduction velocity: computed speed (in meters/second) of nerve conduction of the fastest axon from stimulation to recording
    - Reduced conduction velocities between 70-99% of normal can occur in axonal or demyelinating diseases, but conduction velocities below 70% of normal can only be from demyelination.

CMAP (compound muscle action potential) amplitude: summated voltage response (in millivolts) from the individual muscle fiber action potentials innervated by that nerve

- Are reduced in acute nerve injury
- May be normal in chronic nerve injuries secondary to collateral reinnervation

- When performed well technically, the proximal and distal CMAP amplitude should be almost identical. If the proximal CMAP amplitude drops by >50%, this is conduction block (indicating an acquired demyelinating process) or pseudoconduction block (acute nerve injury). If the proximal amplitude drops by at least 20% with a 30% increase in duration, this indicates abnormal temporal dispersion, which is another indication of an acquired demyelinating process.
- DDx of reduced CMAP amplitude with normal SNAP amplitude: myopathy, presynaptic NMJ (LEMS), radiculopathy, motor neuron disease
- **Distal motor latency**: time interval (in milliseconds) of the fastest axon from distal stimulation to CMAP (indicates speed of distal nerve conduction, NMJ transmission and muscle depolarization)
    - Prolonged distal motor latencies between 100-150% of normal can occur in axonal or demyelinating diseases. **Prolonged distal motor latencies greater than 150% of normal can only occur in demyelinating diseases.**
- Motor Conduction velocity: computed speed (in meters/second) of nerve conduction of the fastest axon from proximal stimulation to distal stimulation
    - Reduced conduction velocities between 70-99% of normal can occur in axonal or demyelinating diseases. **Reduced conduction velocities less than 70% of normal can only occur in demyelinating diseases.**

F waves – evaluate for proximal demyelination that you won't pick up on stimulating/recording sites in the limb. Signal is sent up the motor nerve to the anterior horn cell, then back down the nerve for a recording. Can be useful early sign of GBS if prolonged.

Patterns of injury

Axonal pattern of loss

- Reduced sensory amplitudes without major slowing or other signs of demyelination. Motor amplitudes reduced with severe axonal loss/motor predominant neuropathies.
- Can have some slowing, but should not be below 70% of normal.
- Low CMAP amplitude = seen with any process from the anterior horn cell down

Demyelinating pattern of loss

- Features of demyelination
    - Slowed conduction velocity <70% of normal – Arms <35 m/s, Legs <28 m/s
    - Prolonged distal motor latency -- >150% of normal
    - Conduction block – proximal CMAP amplitude drop of >50% compared to distal recording
    - Temporal dispersion – increased duration of CMAP going from distal to proximal stimulation site -- >30%
    - Increased F wave latency – increased by at least 130-150%
- Note that acquired and inherited demyelinating diseases will have different patterns
    - An inherited demyelinating disease will show diffuse abnormalities in demyelination with uniform slowing in the demyelination range. Less likely to see conduction block and temporal dispersion, which should make you think of an acquired cause (CIDP)

EMG injury patterns

- **Neuropathic** – fibrillation potentials/positive sharp waves (**acute**), large units, reduced recruitment, prolonged duration, high amplitude (**when chronic**)
- **Myopathic –** usually don't see fibs/positive sharp waves unless inflammatory, small units, early full recruitment, low amplitude

NEUROMUSCULAR

Interpreting an EMG report

(material borrowed from CHOP Neurology Handbook)

1. **Start with nerve conduction studies**. Look at SNAPs to determine if injury is proximal or distal to dorsal root ganglion. Lesions proximal to dorsal root ganglion will have preserved SNAPs.
    a. Amplitude is directly proportional to amount of axonal damage. If it's decreased there is injury distal to the dorsal root ganglion (plexus, nerve, multiple nerves). If it's normal then this is a radiculopathy or central.
    b. Think about distribution – if only one nerve is reduced in amplitude you have a mononeuropathy. Multiple nerves indicate a polyneuropathy or mononeuropathy multiplex. Think if pattern could be length dependent.
    c. **Look at SNAP sensory velocities →** are they in the demyelinating range?
2. **Move to CMAP amplitudes**. Note that amplitudes can normalize in 3-6 months after an injury due to collateral innervation so normal may not tell the whole story.
    a. Look for conduction block with reduced proximal motor amplitudes compared to distal motor amplitudes as a sign of acquired demyelination.
3. **Look at motor velocities/distal latencies**
    a. Prolonged distal motor latency > 150% in a single nerve suggests a distal entrapment mononeuropathy (carpal tunnel syndrome or demyelination)
    b. Slow conduction velocity across common sites of compression (ulnar nerve at elbow, peroneal nerve at the head of the fibula, etc) asuggests an entrapment mononeuropathy between the stimulation sites
    c. Widespread slowed velocities should make you think demyelinating when:
        i. Prolonged distal motor latency > 150% or slow conduction velocity <70% in multiple nerves suggests a demyelinating polyneuropathy
        ii. When combined with conduction block or temporal dispersion, these findings suggest an acquired demyelinating condition.
    d. In axonal loss if the fastest and largest axons are injured you can see a mild slowing of conduction velocity and a prolongation of the distal latency but not into the demyelinating range
4. Look at the EMG next
    a. Look at recruitment, then spontaneous activity and motor unit morphology. Reduced recruitment means a peripheral injury
        i. Reduced recruitment and MUAP normal – process is less than a couple months old (collateral innervation has not yet occurred)
        ii. Reduced recruitment with normal MUAP and abnormal spontaneous activity – at least several weeks old
        iii. Reduced recruitment with normal MUAP and no spontaneous activity – acute (<2 weeks)
        iv. MUAP morphology abnormal then process is greater than a couple months as collateral innervation has occurred.
    b. For radiculopathies can see which muscles are showing neurogenic changes and see if these all have a common root

EMG electrical activity

NEUROMUSCULAR

ACTIVITY	DESCRIPTION	CLINICAL SIGNIFICANCE
NORMAL		
Insertional activity	Bursts of spontaneous muscle response with insertion of needle (lasts several hundred milliseconds)	None
Endplate noise	Recurring, *irregular* negative potentials (10-50 uV lasting 1-2 ms) produced by spontaneous release of Ach (non-conducting)	None, normal at motor end plate
Endplate potentials	*Irregular* negative potentials (100-200 uV lasting 3-4 ms) produced by spontaneous firing of single muscle fibers from needle irritation	None, normal at motor end plate
ABNORMAL		
Fibrillation potentials/positive sharp waves	*Regular* (1-30 Hz) spontaneous negative potentials (20-200 uV lasting 1-5 s) of denervated single muscle fibers	Arise when an individual muscle fiber is no longer innervated (nerve injury or inflammatory myopathy; Fibs arise 2-3 weeks after axonal loss
Fasciculation potentials	*Irregular*, spontaneous discharges of a motor unit	Seen most commonly in anterior horn diseases (e.g. ALS), but also in radiculopathies, entrapment neuropathies, & polyneuropathies (also seen in normal people, but usually at a faster firing rate)
Myotonic discharges	A type of abnormal insertional activity characterized by spontaneous independent repetitive potentials arising from singular muscle fibers; Evoked by needle insertion, movement, or voluntary contraction	Seen in MD1 and MD2, acid maltase deficiency, myotonia congentita, hyperkalemic periodic paralysis, colchicine myopathy, glycogen storage diseases (e.g. Pompe) & myotubular myopathy
Myokymia	Complex bursts of repetitive motor unit discharges (2-10 spikes at 30-40 Hz) recurring at 1-5 s intervals; Evoked by motor axon	Seen in brainstem gliomas and MS (if facial muscles involved), or radiation plexopathies
Complex repetitive discharges	Multiphasic firing of a group of muscle fibers (appear as grouped fibrillations) up to 100 ms; Distinguish from myokymia in that the firing pattern of CRDs is identical	Etiologically non-specific
Neuromyotonic discharges	Repetitive high-frequency (150-250 Hz) firing of muscle fibers thought to be due to abnml CASPR2	Seen in Isaac's & Morvan's syndrome (autoimmune neuropathy), AchE poisoning, tetany, SMA

Ordering EMG/NCS at HUP:

For inpatient EMG/NCS, place order in Epic and call EMG lab at 215-360-0271, usually can be done within 1-2 days.

For outpatient EMG/NCS, place order in Epic. Scheduler will call patient to arrange. Performed at HUP for resident clinic. Helpful to put in comment what limbs you want tested

NEUROMUSCULAR

EMG/NCS normal values

Normal Values

Motor Nerve Conduction Studies

Nerve	Distal Latency (ms)	Conduction Velocity (m/s)	Amplitude (mV)	F Latency (ms)
Peroneal (EDB)	≤ 6.5	≥ 41	≥ 2.0	≤ 56
Peroneal (TA)	≤ 6.7	≥ 41	≥ 5.0	≤ N/A
Tibial	≤ 5.8	≥ 41	≥ 4.0	≤ 56
Median	≤ 4.4	≥ 49	≥ 4.0	≤ 31
Ulnar	≤ 3.3	≥ 49	≥ 6.0	≤ 32
Radial	≤ 2.9	≥ 49	≥ 2.0	≤ N/A

Sensory Nerve Conduction Studies

Nerve	Conduction Velocity (m/s)	Amplitude (μV)
Sural	≥ 40	≥ 6
Superficial peroneal	≥ 40	≥ 6
Median (orthodromic)	≥ 50	≥ 10
Ulnar (orthodromic)	≥ 50	≥ 7
Radial	≥ 50	≥ 15

Median-Ulnar Nerve Comparison Studies

Nerve	Segment	Distance	Normal Latency Difference (ms)
Median mixed nerve	Palm to wrist	8 cm	
Ulnar mixed nerve	Palm to wrist	8 cm	≤ 0.4

The Mononeuropathies

Axillary Neuropathy

Findings: arm abduction weakness (deltoid), numb patch on lateral upper arm
Differentiate from:

1. C5 radiculopathy or upper trunk (sparing of shoulder external rotation and arm flexion)
2. Posterior cord (sparing of arm and finger extension)

Usual Etiology: Dislocation of proximal humerus

Musculocutaneous Neuropathy

Findings: arm flexion weakness (bicep), decreased bicep reflex; numb area on lateral arm and forearm
Differentiate from:

1. C5 radiculopathy (sparing of shoulder external rotation, arm abduction, arm flexion when half-prone)
2. C6 radiculopathy (sparing of shoulder external rotation, arm abduction, arm flexion when half-prone, no numbness over thumb and index finger)
3. Lateral cord (sparing of arm pronation, no numbness over thumb and index finger)

Usual Etiology: trauma – gunshot to upper arm, tourniquet left on upper arm - (rare)

Radial Neuropathy

Findings:

1. At the wrist – just causes sensory loss over part of the dorsal hand, no motor sx.
2. Posterior interosseous neuropathy: **no sensory loss**, weak finger and wrist extensors; weak supinator, brachioradialis strength and reflex usually spared.
3. At the spiral groove: numb area over dorsal hand (variable size); weak finger and wrist extensors; weak supinator; weakness of the brachioradialis (but not biceps); depressed brachioradialis reflex
4. Proximal to spiral groove: as above plus weak triceps with depressed triceps reflex; also may have numb strip down posterior arm and forearm

Differentiate from:

1. C7 radiculopathy (common) or middle trunk lesion (rare) – (sparing of arm pronation and no numbness over palmar aspect of middle finger)
2. posterior cord lesion (by sparing of arm abduction)

Usual Etiology:

1. radial neuropathy at the spiral groove (common): often occurs with intoxicated sleep (with the arm over a chair, stool or hand surface). Commonly mistaken for stroke. "Saturday night palsy"
2. radial neuropathy at the wrist: handcuffs - "handcuff neuropathy"
3. radial neuropathy at the axilla: improper use of crutches (pressing up into axilla)

Exam tips:

1. triceps strength and reflex are key to localizing the lesion along the radial nerve
2. ulnar intrinsic hand muscles may *appear* weak since it is hard to abduct the fingers if you can't extend them; test intrinsic hand muscles by placing the hand on a flat, firm surface

Median Neuropathy

Findings:

1. At the wrist – Carpal Tunnel Syndrome – CTS – pain and sensory loss in thumb, index, middle fingers; weakness of thumb abduction
2. Anterior interosseous neuropathy: weakness of distal thumb flexion and index finger flexion (cannot make an "ok" sign, no sensory loss)
3. Proximal (usually near elbow): as above *plus* weak arm pronation.

Differentiate from:

1. C6 radiculopathy – sparing of arm external rotation, arm flexion when half-prone, normal biceps and brachioradialis reflexes.
2. C8/T1 radiculopathy – sparing of finger abduction and no numbness on small finger or medial forearm

Usual Etiology:

1. CTS: usually idiopathic, worse in dominant hand, worse with hand use.
2. Rarely associated with acromegaly, amyloidosis, arthritis, wrist trauma, connective tissue diseases, etc. Frequently associated with diabetes.

Exam tips:

1. Median nerve has a C6 area of sensation, but the hand muscles are C8/T1 – so it is easily distinguished from radiculopathies
2. CTS tricks: Tinnel's sign (percussion over carpal tunnel elicits the pain) and Phalen's sign (press the backs of the hands together with wrists hyper-flexed → elicits pain)
3. Differentiate CTS from proximal median neuropathy by testing proximal median muscles: be sure pronation is strong (pronator teres)

Treatment of CTS:

-If patient is pregnant generally treat with wrist splinting, CTS should resolve after delivery
-If symptoms are mild (sensory symptoms without abnormalities on exam) you can do splinting

-If symptoms are moderate to severe (numbness or weakness or ADL disruption) refer for EMG. If there is evidence of axonal loss or denervation then refer for surgery (Ortho-hand referral)

Ulnar neuropathy

Findings:

1. At the elbow (cubital tunnel syndrome) –weakness of medial wrist flexion, distal ring and small finger flexion, finger abduction, numb over dorsal and palmar hypothenar eminence, ring and small finger.
2. At the wrist – just the intrinsic hand muscles are weak. Numb over the palmar hypothenar eminence, ring and small finger only.

Differentiate from:

1. C8 or T1 radiculopathies – sparing of thumb abduction, index finger extension and medial forearm numbness.
2. Lower trunk: sparing of thumb abduction, index finger extension and medial forearm numbness.
3. Median cord - sparing of thumb abduction and medial forearm numbness.

Usual etiology:

1. compression at the elbow is very common.

Exam tips:

1. be cautious if you detect numbness above the wrist – the ulnar nerve should not do that
2. if the fingers extensors (radial) are weak, you need to support the hand by placing it flat on a table to test the ulnar intrinsic hand muscles – place the hand flat on the table, palm down, and then have the patient spread the fingers.

Treatment for ulnar neuropathy at the elbow:

-avoid prolonged leaning on elbow or prolonged elbow flexion

-data on splinting of elbow is poor, low cost way to replicate is to wrap elbow with towel at night to limit flexion

-Surgical referral for patients with clear weakness and EMG evidence of significant axonal loss. Presence of symptoms for several years and severe involvement will generally to poor with surgery. Cubital tunnel release is not as effective as carpal tunnel release is for CTS.

Obturator neuropathy

Findings: weak thigh adduction and medial thigh numbness

Differentiate from:

1. Lumbo-sacral plexopathy – sparing of hip flexion, knee extension, no anterior or lateral thigh numbness.
2. High lumbar radiculopathy (L3/4) – sparing of hip flexion, knee extension, no anterior or lateral thigh numbness.

Usual etiology:

1. child birth injuries

Femoral neuropathy

Findings:

1. At the inguinal ligament – weakness of knee extension, numbness over part of anterior thigh, depressed knee jerk reflex.
2. Very proximally –also weakness of hip flexion

Differentiate from:

1. Lumbo-sacral plexopathy – sparing of hip aDDuction and no medial or lateral thigh numbness.
2. High lumbar radiculopathy (L3/4) – by sparing of hip aDDuction and no medial or lateral thigh numbness.

Usual etiology:

1. Inguinal: think of all the sharp things you saw placed near the inguinal ligament during internship...
2. Proximal: consider retroperitoneal hemorrhage or mass, or plexitis.

Exam tips:

1. Carefully check the knee jerk reflex versus the other side.
2. Carefully check hip ADDuction.
3. Important to decide if psoas is involved or not

Peroneal neuropathy

Findings:

1. Deep peroneal nerve: weakness of toe extension and foot dorsi-flexion (foot drop), numbness between the great and 2nd toe webspace.
2. Superficial peroneal: weakness of foot eversion (leads to tendency to fall and twist ankle), numbness over the lateral calf and dorsal foot.
3. Common peroneal nerve: all of the above. Local pain may be present at fibular head

Differentiate from:

1. Sciatic neuropathy– peroneal neuropathy with sparing of ankle inversion and ankle plantarflexion, no numbness on posterior calf or sole, preserved ankle jerk w/ peroneal neuropathy (can have preferential peroneal division in sciatic neuropathy, which cannot be differentiated from common peroneal neuropathy above the head of the fibula)
2. Lumbo-sacral plexopathy – sparing of ankle inversion, ankle plantarflexion, and hip aBDuction, no numbness on posterior calf or sole, reduced ankle jerk w/ peroneal neuropathy
3. L5 radiculopathy– sparing of ankle inversion and hip aBDuction

Usual etiology:

1. Compression at the fibular head is common from trauma, crossing legs, in bed-bound patients (esp if sedated).

Exam tips:

1. To test inversion (the tibial L5 muscle that is so useful for distinguishing L5 radiculopathy from peroneal neuropathy), you need to support the foot in dorsi-flexion. If you allow patient to do this while plantar-flexed invasion may appear strong secondary to medial gastroc compensation
2. Also, carefully test tibial plantar flexion and ankle-jerk reflex.

Tibial neuropathy

Findings:

1. weak plantar flexion, ankle inversion, suppressed ankle-jerk, numbness over posterior calf and sole

Differentiate from:

1. sciatic neuropathy: sparing of ankle dorsiflexion, eversion, toe extension, and knee flexion no lateral calf or dorsal foot numbness
2. Lumbo-sacral plexopathy: sparing of ankle dorsiflexion, eversion, knee flexion, toe extension, hip extension, and hip abduction
3. S1 radiculopathy: sparing of knee flexion and hip extension

Usual etiology:

1. Trauma, popliteal cyst

Exam tips:

1. Test the gluteus maximus (proximal S1 muscle) to distinguish from S1 radiculopathy

Polyneuropathy

NEUROMUSCULAR

Polyneuropathies are one of the most common referrals to resident clinic. Often times there will be an identifiable etiology in history (DM most commonly) and the patient may be referred to help with symptom management. When there is no identifiable cause the goal of the evaluation is to:

1) look for an obvious underlying etiology that is potentially treatable with a set of screening labs
2) if no clear answer on first pass, then classify the neuropathy as an axonal or demyelinating process and then proceeding with further workup down either path
3) identifying which patients may benefit from genetic testing
4) treating neuropathy related symptoms – in most cases this the best we can do as few treatments exist to reverse previous nerve damage).

Clinical Manifestations/Diagnosis of a distal, symmetric polyneuropathy: A homogenous process affecting many peripheral nerves at once, in a length dependent fashion. Characterized by time course, presentation, and progression (see chart). Can impact large fibers (motor, vibration/proprioception) or small fibers (pinprick and temperature). Must account for predisposing factors (DM, toxic exposures, ETOH, HIV/ESRD, co-existing autoimmune diseases). Almost 50% of cases will be idiopathic after a full evaluation.

Workup:

- **If there is a clear underlying etiology** (such as diabetes mellitus, alcohol use disorder, prior chemotherapy) then you can treat symptomatically and do not need to pursue a full workup including EMG/NCS.
- **If you do not already know about a clear underlying etiology** and the patient's history/exam is consistent with a polyneuropathy you should send off (per AAN recommendations): CMP, A1c, B12 with MMA, SPEP with immunofixation (make sure you order both or ensure that immunofixation is specified in comments)
  - *Can also consider: HIV, ESR, Thiamine, TTR (for amyloid, now a treatable condition so worth screening for).

-NOTE: the above screening tests are for a relatively indolent, symmetric, polyneuropathy that is sensory >> motor.

Do I need to do an EMG/NCS for every neuropathy referral?

- Not necessarily! If you know the cause (diabetes, chemo) and they have an indolent/stable sensory predominant length dependent neuropathy on exam then an EMG is of little utility.
- You can also argue that even if the above tests are negative but on exam they have intact reflexes but some mild diminished pinprick distally you can also defer an EMG and treat symptomatically and monitor with serial exams as the EMG/NCS is unlikely to give useful information if you suspect only a small-fiber neuropathy.

Indications for a more in-depth workup (AKA Neuropathy Red Flags): Asymmetric, non-length dependent, motor predominant, acute onset, primarily autonomic, rapidly progressive, sensory ataxia, onset at age < 50

- EMG/NCS: helps to determine axonal versus demyelinating features, peripheral nerve versus muscle, or radiculopathy
- Further laboratory testing (in addition to above) based on EMG/NCS results

  Axonal polyneuropathy

  ANA, RF, SSA/B, Anti Hu (sensory neuronopathy) , Lyme testing, B1, Hepatitis B and C, Urine/blood heavy metals and urine/blood porphyrins

  Demyelinating polyneuropathy

  Hepatitis B and C, Anti-MAG antibodies (predom sensory ataxia), Anti-GM1 antibodies (predom motor), VGEF, Genetic testing for CMT (if history/EMG suggestive of inherited demyelinating neuropathy)
- Nerve/Muscle Biopsy: mainly useful if amyloid or vasculitis is suspected
- Genetic testing: Hereditary cause suspected (see section on genetic testing)

NEUROMUSCULAR

Differential diagnosis of polyneuropathies

Systemic disease	Axonal vs Demyelinating		Timecourse			Sensory vs. Motor
Common	**Axonal**	**Demyelinating**	**Acute**	**Subacute**	**Chronic**	
Diabetes	+	-	-	±	+	S, SM
Uremia	+	-	±	+	+	SM
Chronic liver disease	+	-	-	-	+	S or SM
Critical illness	+	-	-	+	±	M > S
HIV	+	-	-	±	+	S >> M
Less common						
B12 deficiency	+	-	-	±	+	S
Amyloidosis	+	-	-	±	+	SM
Vitamin B6 intoxication	+	-	-	+	+	S
Malabsorption/celiac	+	-	-	±	±	S or SM
Multiple myeloma/MGUS	+	+	-	±	+	SM
Sjogrens	+	-	-	±	+	SM or S
AIDP	-	+	+	-	-	M>S
CIDP	-	+	-	±	+	SM>S
Rare						
Distal Acquired Demyeinating Syndrome (DADS) IgM to MAG	-	+	-	±	+	S>SM
POEMS*	-	+	-	±	+	SM
Anti-Hu	+		-	±	+	S
Porphyria (4 types)	+	-	+	±	-	M or SM
CMT	+	+	-	-	+	SM
Mitochondrial	+	_	±	±	±	SM

Acute	AIDP (GBS), AMAN (very fast, axonal motor-only GBS), vasculitis, porphyria, toxins (organophosphates, arsenic, thalidomide), tick, drugs, acute thiamine deficiency, critical care neuropathy

Stepwise (mononeuritis)	Vasculitis: PAN, Sjogren, Churg-Strauss, Wegener's, hypersensitivity cryoglobulinemia, SLE, RA, isolated PNS vasculitis DM CIDP (MADSAM variant) Infectious: Lyme, HIV, HepC/ cryos, leprosy Infiltration: (sarcoid (esp. b/l facial nerve), lymphoma)
Predom motor	lead, porphyria, some hereditary, AIDP/CIDP, multifocal motor neuropathy (MMN), dysproteinemia
Pure sensory	paraneoplastic (anti-Hu), Sjogren, toxic (cisplatin, B6), HIV, anti-sulfatide Ab, Friedreich's, idiopathic, hereditary (HSN)
Predom autonomic	AIDP, DM, amyloid * toxins concentrated in urine can affect the bladder worst (e.g. cisplatin)
Small-fiber neuropathy	DM, amyloid, toxic (EtOH), hereditary, Tangier, Fabry, AIDS, idiopathic
Demyelinating	Acute: AIDP Sub-acute: CIDP, lead, POEMs Chronic: CIDP, DADS, CMT1, HNPP

Symptomatic treatment of neuropathic pain

NOTE: set expectation that pain is unlikely to completely resolve but should improve, though may not improve for several weeks – important to reach therapeutic doses of drug before considering it a failure

1) Gabapentin/pregabalin – require renal dosing
   -Gabapentin – 100 to 300 mg daily to TID. Titrate up slowly in 300 mg steps to 1800 to 3000 mg daily divided TID
   -Pregabalin – 25 to 75 mg daily, can titrate up in steps of 75 mg per week to 150 mg BID or 100 mg TID
2) SNRIs -- reach for in older patients given poor tolerability of TCAs
   -Duloxetine – 20/30 mg daily and titrate up to 60 mg daily
   -Venlafaxine – 37.5 mg daily and titrate up to 75 to 225 mg daily
3)Tricyclic antidepressants – amitriptyline or nortriptyline (can use in younger patients without a cardiac history and with trouble sleeping)
   -Start at 10-25 mg pe day with gradual titration up to 100 mg/day. The older the patient is the lower and slower you should go
4) Sodium channel blockers (i.e. oxcarbazepine, lamotrigine)

NOTE: opioids/tramadol not very good options for neuropathic pain, in our clinic you should avoid using these! If patient fails all of our options you can refer to pain management.

Sampler of Etiologies

GUILLAIN-BARRE SYNDROME

Presentation: acute-subacute ascending motor/sensory loss with arrefelxia, often with pain (nerve root inflammation). Can be presceded by GI symptoms (campylobacter) or URI symptoms. Impacts 1-4/100,000 annually. The term GBS really refers to a collection of acute immune mediated (molecular mimicry?) polyneuropathies. While these are typically thought to be demyelinating, they can be axonal as well. There can be variable presentations. Weakness typically starts in legs but can be in arm/face in 10%, see facial nerve palsies in 50%. Decreased/absent

reflexes seen in 90% of patients at presentation. Dysautonomia common (70%). Nadir of disease typically occurs at week 4, continued progression indicates CIDP.

Diagnosis: Note that not all of the below studies need to be completed to make the diagnosis of GBS (i.e. an EMG early in disease course may not show evidence of demyelination, treatment can start with right clinical presentation/LP findings). Second, not every patient suspected of having GBS needs inpatient admission/treatment – i.e. mild symptoms several weeks after presentation – likely will improve on their own.

1) *Respiratory status*: check vital capacity (VC) and negative inspiratory force (NIF). May be misleading of facial weakness leads to poor seal. VC below 15 cc/kg and NIF below 30 cm H2O very concerning. Consider admitting to NICU for closer respiratory monitoring given possibleneed intubation unless trending upwards. Hypoxia can lag behind hypoventilation. -Estimate VC with single breath count – e.g. counting to 25 = 2.5 liters VC.
2) *Try to do LP as soon as able*: Looking for albuminocytologic dissociation (normal cells, high protein). Finding present in 50-60% of patients with GBS in first week after symptom onset and in >75% by week 3. High protein may be from increased blood brain barrier permeability at nerve roots. Typically, normal protein = age in years. Elevated cells can occur – between 5-50 – only in 15% of patients though. If pleocytosis: think of GBS + HIV.
3) *Send off serum labs to exclude underlying cause/identify causative antibody:* Ganglioside antibotides (GM1, GM1b, GD1a, GQ1b), HIV, Lyme (in right clinical context), B12/thiamine always good to check, SPEP with IFE, spot urine porphobilinogen with urine creatinine with abdominal pain/recurrent bouts of neuropathy (porphyria)
4) *Check EMG*: this should not delay therapy, in an early non-severe case with convincing story/exam/LP can argue it isn't needed on inpatient basis. Looking for demyelinating features (slowed conduction, conduction block, prolonged distal motor latency, temporal dispersion, **increased F wave latency (may be first sign)).** Repeat examinations are often useful especially if there is diagnostic uncertainty. Per Dr. Bird, you can never do an EMG too early or too often for GBS

Variants: Remember, GBS is a heterogenous disorder that wears many outfits. The unifying nature is a presumed autoimmune cause and an acute time course.

- **Acute inflammatory demyelinating polyneuropathy (AIDP)**: This is what we mean by classic GBS – represents about 90% of cases (the above discussion applies to AIDP).
- **Acute motor axonal neuropathy (AMAN):** Selectively involves motor nerves and shows an axonal pattern on EMG. Occasionally have preserved reflexes. Progresses rapidly but prognosis similar to AIDP. Prevalent in Asia and more common in summer. Pathogenesis felt to be antibody/complement mediated damage of axons.
- **Acute motor and sensory axonal neuropathy (AMSAN)**: more severe than AMAN, impacting motor and sensory nerves with axonal damage/degeneration. See severely reduced motor and sensory responses. With recovery will see signs of denervation/re-innervation on EMG.
- **Miller Fisher Syndrome**: A classic syndrome of ophtalmoplegia, ataxia, areflexia with ¼ also showing extremity weakness. Syndrome can also be incomplete. See antibodies against GQ1b in 90%. EMG may show features c/w demyelination.
- **Bickerstaff encephalitis**: brainstem encephalitis with encephalopathy and increased reflexes along with features of Miller Fisher Syndrome. Can see in association with anti-GQ1b antibodies.
- **Pharyngeal cervical brachial weakness:** Can overlap with Miller Fisher/Bickerstaff. Acute weakness of oropharyngeal, neck, shoulder muscles with swallowing dysfunction. Can see antibodies against GT1a, GQ1b, GD1a.
- **And many more** (acute pandysautonomia, pure sensory GBS...)

Brighton criteria for case definition of Guillain-Barré syndrome

Level 1 of diagnostic certainty	Level 2 of diagnostic certainty	Level 3 of diagnostic certainty
▪ Bilateral and flaccid weakness of the limbs; **AND** ▪ Decreased or absent deep tendon reflexes in weak limbs; **AND** ▪ Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; **AND** ▪ Absence of identified alternative diagnosis for weakness; **AND** ▪ Cytoalbuminologic dissociation (ie, elevation of CSF protein level above laboratory normal value and CSF total white cell count <50 cells/microL; **AND** ▪ Electrophysiologic findings consistent with GBS	▪ Bilateral and flaccid weakness of the limbs; **AND** ▪ Decreased or absent deep tendon reflexes in weak limbs; **AND** ▪ Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; **AND** ▪ Absence of identified alternative diagnosis for weakness; **AND** ▪ CSF total white cell count <50 cells/microL (with or without CSF protein elevation above laboratory normal value); **OR** electrophysiologic studies consistent with GBS if CSF not collected or results not available	▪ Bilateral and flaccid weakness of the limbs; **AND** ▪ Decreased or absent deep tendon reflexes in weak limbs; **AND** ▪ Monophasic illness pattern; and interval between onset and nadir of weakness between 12 hours and 28 days; and subsequent clinical plateau; **AND** ▪ Absence of identified alternative diagnosis for weakness

CSF: cerebrospinal fluid; GBS: Guillain-Barré syndrome.

Treatment:

- IVIG or plasma exchange – <u>note that steroids are not effective for GBS</u>
  - IVIG: order 0.4 gm/kg/day x 5 doses, requires consent for pooled blood products. Can give Tylenol 650 mg, Benadryl 25 mg before infusion for premedications. Risks include thrombotic events, volume overload, aseptic meningitis and is contraindicated in IgA deficiency.
  - Plasma Exchange: 5 treatments over 10, needs aphesis catheter placed – procedure team can help. Risks include hypotension, line sepsis, complications related to placement of apheresis catheter, bleeding
- IVIG and PLEX are most effective in the first 2-4 weeks after symptoms onset
- No evidence that combining IVIG and plasma exchange leads to greater benefit than either therapy alone

Outcomes:

- Mortality rate is around 5%. 60-80% can walk at 6 months. Certain factors can predict a more severe disease course:
  - <u>Predictors of disability:</u> Absence of motor response or axonal involvement on EMG, can't walk at 14 days, rapid progression, severity of symptoms at peak, older age, prior diarrhea/CMV infection.

- Studies show that initiating disease modifying therapy generally improves recovery of motor milestones by a couple weeks and can increase likelihood of a full recovery at one year
- Be aware that about 5% of AIDP patients will progress to CIDP – look for worsening after the 8 week mark to help differentiate between the two.

GBS and vaccines:

1) Can my GBS patient get the flu vaccine?
   Answer: The general advice is to avoid the flu vaccine if the prior case of GBS started within 4 weeks of getting a flu vaccine. In reality, outside of the swine influenza vaccine in 1976, where there was an 8 fold increase in GBS cases, the risk carried by yearly flu vaccines is very minimal and pales against the risk posed by the flu infection. For instance, within 90 days after an influenza like illness the relative incidence of GBS increases more than 5 fold (data from Britain). Therefore, for most patients with prior GBS it is sound advice to recommend the yearly flu vaccine.
2) Related: can my patient get the COVID vaccine?
   Answer: Unless their GBS started within 4 weeks of a prior vaccination. Then a more nuances risk/benefit discussion is appropriate.

CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

Presentation: gradual onset of symmetric, progressive, sensorimotor polyneuropathy over course of several months/year. Thought to be caused by autoimmune response against nodal/paranodal proteins leading to demyelination. Some patients present more rapidly and mimic AIDP but continue to progress after 8 weeks. Weakness *may be present in non-length dependent fashion*. The combination of proximal weakness and distal sensory loss is highly suggestive of CIDP. Cranial nerve and bulbar involvement seen in 10-20%. Autonomic involvement not as common with CIDP as with AIDP.

Diagnosis: For full diagnostic criteria refer to the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS) criteria. The following criteria generally support the diagnosis of CIDP:

Progression over two months. Weakness more than sensory symptoms. Symmetric involvement of arms and legs. Proximal muscles involved along with distal muscles. Reduced DTRs throughout. Increased CSF protein without pleocytosis (less than 10 WBCs). NCS evidence of demyelinating polyneuropathy. Nerve biopsy evidence of segmental demyelination.

Common Pitfalls: When you are working in the Attending urgent care clinics you may get patients who have been told they have CIDP and are being treated with IVIG. You should be careful and do your best to confirm their diagnosis because CIDP is an often over-diagnosed disease based on the following:

1) Diagnosing "small fiber CIDP" when patient has normal exam/NCS but an idiopathic neuropathy based on symptoms – this is incorrect as the smallest nerve fibers do not have myelin and cannot be demyelinated.

2) Overcalling demyelination on NCS – calling mild slowing demyelination or calling demyelination at common sites of compression.

3) Overinterpreting mild CSF protein elevation without correct clinical context

Variants/other demyelinating neuropathies:

- **Asymmetric sensorimotor (multifocal):** Lewis-Sumner Syndrome or **MADSAM** (multifocal acquired demyelinating sensory and motor neuropathy) – looks like a mononeuritis multiplex

- **Patchy/asymmetric weakness**: Multifocal motor neuropathy (MMN). Multifocal asymmetric regions of partial conduction block on EMG with GM1 antibody in serum. Normal CSF. Treat with IVIG or cytoxan. Can sometimes be mistaken for ALS
- **Distal and sensory predominant: DADS** (distal acquired demyelinating symmetric polyneuropathy) – slowly progressive. Very prolonged distal latencies. More likely to have a monoclonal gammopathy (IgM) w/ anti-MAG antibodies. Often resistant to treatment when a monoclonal gammopathy is present.
- **Neurofascin and Contactin antibody mediated:** select group of patients with autoantibodies to nodal/paranodal antigens. May respond better to B cell depletion with Rituximab

Treatment:

1)Initial therapy

- Severe/fulminant disease – IVIG vs plasma exchange
- Insidious – Steroids vs IVIG

If steroids are contraindicated then another immunosuppressive agent can be used, like methotrexate, Mycophenolate, or azathioprine, although their effectiveness has not been proven in CIDP. If you have a patient who is progressing and accruing disability if would be best to consult with the neuromuscular attendings and consider a heavier hitting immunotherapy like cytoxan

2)Monitoring

- At least every 3 months when starting therapy, then a couple times per year on maintenance therapy.

3)Duration of therapy

- 30% will achieve remission after starting their initial therapy and treatment can be weaned off after a sustained remission over a year.
- Relapses can be treated by going back up on therapy (increasing dose of steroids/frequency of IVIG).
- Patients on IVIG may benefit from adding on another agent (steroids etc) in an attempt to wean down frequency of IVIG

PARAPROTEIN RELATED NEUROPATHIES

Paraproteins are abnormally produced proteins that can be detected via SPEP/UPEP and can either be present in asymptomatic individuals (MGUS) or with a variety of malignancies (Multiple Myeloma, Waldenstroms, etc). Amyloidosis can also fit into this broader category. Sometimes a patient will have a neuropathy with a clear relationship to one of the etiologies listed below, however, given the prevalence of both neuropathy and MGUS in the elderly population, you may also see patients whose neuropathy is not clearly related to their paraprotein. Teasing apart this distinction requires matching clinical presentation/EMG findings with known clinical syndromes and associations. Many of these patients will need to be comanaged/evaluated by Heme/Onc.

Monoclonal gammopathy of undetermined significance (MGUS): asymptomatic clonal plasma cell disorder characterized by presence of serum monoclonal protein (M protein) but low level of monoclonal B cells in blood and no end organ damage. Progress to malignancy at a rate of 1% per year. Has 3 different flavors (outlined below) that have different associations with neuropathy. In patients with neuropathy, the most common monoclonal protein is IgM (50%), IgG (35%), IgA (15%).

If you suspect your neuropathy patient may have MGUS you should send off a CBC, calcium, CMP, SPEP/UPEP (if not already done), serum free light chains, quant immunos, and referral to Heme/Onc.

- **Non-IgM MGUS (IgG, IgA, IgD)** -- most common type of MGUS, can progress to MM or AL amyloidosis
  - -With exception of POEMS (see below), a demyelinating neuropathy with an IgG or IgA paraprotein acts like CIDP without a paraprotein and shows a similar response to treatment

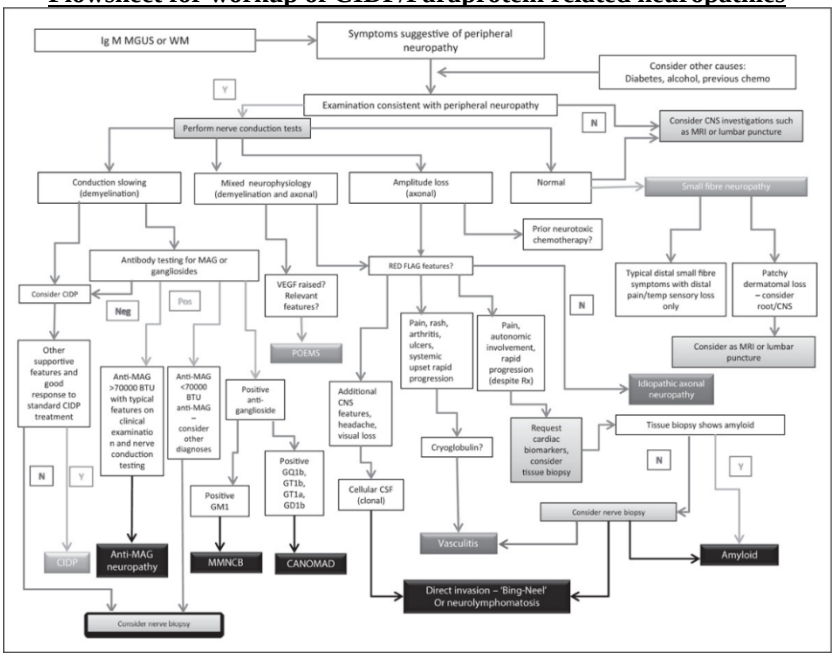
- **IgM MGUS** – 15% of MGUS cases. Can progress to Waldenstrom macroglobulinemia (see below) or IgM MM.
  -IgM is related to demyelinating neuropathies and can cause a distal acquired demyelinating symmetric neuropathy (DADS, see above). Anti-MAG antibodies are IgM antibodies that are present in up to 50% of patients with IgM paraproteins and a DADS phenotype.
- **Light chain MGUS** – may progress to AL amyloidosis or light chain deposition disease

POEMS: Polyneuropathy, organomegaly, endocrinopathy, M-protein (usually IgG, IgA, rarely IgM), skin changes. Consider in patients with a demyelinating/axonal peripheral neuropathy on EMG. Neuropathy is distal and symmetric with sensory/motor involvement. Look for elevated levels of VGEF. CSF shows elevated protein. There is no standardized therapy.
Waldenstrom macroglobulinemia: slow growing lymphoplasmacytic tumor that warrants treatment when it causes systemic effects, like neuropathy. Can produce IgM monoclonal proteins that can be Anti-MAG. Typically in 7th decade and can present with hyperviscocity of blood due to high levels of monoclonal proteins. 20% will have neuropathy at time of diagnosis. Given IgM relationship neuropathy most often demyelinating. Can treat with plasma exchange, IVIG or B cell depletion with Rituxan.
Amyloidosis: Amyloidosis is a term for extracellular tissue deposition of low molecular weight subunits of normal serum proteins. Diagnosed via histo examination of skin/nerve with Congo red stain or kappa/lambda immunohistochemical staining. Look for cardiac, liver, kidney involvement. There are several types of amyloidosis, but not all are associated with neuropathy:

- **AA amyloidosis**: complication of chronic disease with ongoing inflammation. Serum amyloid A protein (acute phase reactant) deposits in tissue. **RARELY affects the peripheral nervous system.**
- **AL amyloidosis**: caused by plasma cell/B cell disorders. Abnormal cells make heavy/light chains which deposit in tissue creating amyloid fibrils. See peripheral neuropathy in almost 20% of patients with AL amyloidosis. **Pattern is a sensorimotor axonal polyneuropathy, compressive neuropathies (CTS), and autonomic neuropathies.** Treat with chemotherapy or stem cell transplant.
- **Familial amyloid polyneuropathy**: group of hereditary amyloidosis with prominent peripheral nervous system involvement. Most common amyloid protein involved is transthyretin (TTR), hence why we often test the *TTR* gene for mutations (Val30Met is most common pathogenic point mutation). Neuropathy can be compressive, length depending sensorimotor polyneuropathy with pain (axonal pattern), or autonomic. Treatment for neuropathy are siRNA/antisense oligonucleotides (patisiran, inotersen, vutrisiran). Patients often have co-existing cardiomyopathy so referral to cardiology is needed.
  - **NOTE**: **if you want to perform a fat pad biopsy** on an outpatient while they are in clinic place order for "Fat Pad aspirate" and pathology will come perform the procedure while the patient is still in clinic!

Cryo related neuropathy: Cryoglobulins are immunoglobulins that precipitate in cold/dissolve when rewarmed. Can affect multiple organs by depositing as antigen-antibody complexes in arteries. Can be associated with hep C/hep B, chronic autoimmune conditions. Can cause a painful sensory neuropathy, sensorimotor axonal neuropathy, or a mononeuropathy multiplex due to ischemic from deposition in arteries. Lab testing will show low complements. Need to identify underlying etiology and treat that. Can also treat with steroids/rituxan/cytoxan/PLEX.

Flowsheet for workup of CIDP/Paraprotein related neuropathies



From Lunn, Neuropathies and paraproteins. Current opinion in Neurology 2019.

CANOMAD = chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins, and disialosyl antibodies
MMNCB = Multifocal motor neuropathy with conduction block

NUTRITIONAL/METABOLIC NEUROPATHIES

Diabetes mellitus: typically a distal symmetric sensory polyneuropathy. Large myelinated fibers (causing vibration/proprioception issues) and small nerve fibers (pain and temp issues) are affected. Prevalence increases with duration of disease and eventually will affect at least 50% of everyone with diabetes. Should suspect diabetes as culprit in patient with T1DM of more than 5 years and in all patients diagnosed with type 2 (very likely had diabetes for prolonged period of time prior to diagnosis). Improved glycemic control prevents progression in T1DM but this effect is not seen with T2DM.

- **What about patients with neuropathy and prediabetes?** Polyneuropathy is seen much more frequently in patients with pre-diabetes versus not (40-50% for prediabetes versus 14% of age matched controls). If your patient with pre-diabetes has what sounds like a painful diabetic polyneuropathy on physical exam then you can attribute it to the pre-diabetes, but should exclude other common causes (like B12 deficiency).
- **When to exclude other causes?** Asymmetric, rapidly progressive, motor worse than sensory involvement

B12 deficiency: can be seen in vegans/vegetarians who are not taking B vitamins, people who have had gastric bypass/sleeves and aren't taking their vitamin supplementation. Deficiency typically evolves over years following depletion of total body stores. Causes a symmetric length

dependent neuropathy along with subacute combined degeneration of the spine. Neuropsych manifestations can be seen as well. Causes macrocytic anemia. Test for serum B12 levels and MMA (accumulates with B12 deficiency) - if MMA elevated but B12 normal then still want to treat.. If symptomatic or concerns for absorption then correct quickly with IM injections.

Thiamine (B1) deficiency: absorbed in jejunum/ileum. Body has two weeks of stores, symptoms can develop one week after poor intake. Rare in developed countries but can occur in alcoholism, bariatric surgery, TPN, or with excess losses from chronic diarrhea. Can be "dry" and cause peripheral neuropathy or "wet" and cause cardiomyopathy. Should test for deficiency with a whole blood thiamine level STAT and treat urgently with 500mg IV three times daily for at least 2 days. If there is no concern about W-K then you can treat with 100mg orally per day for at least 1 month. Neuropathy improvement will be slow. Do not wait for levels to result before treating.

B6 (pyridoxine) toxicity: long term intake of over 250 mg per day can lead to peripheral neuropathy/sensory neuronopathy (typically we only need about 1-2 mg per day). Can happen when people take whopping doses of B-vitamins in pills (as OTC vitamins or in conjunction with isoniazid or with excessive energy drink intake. Can also cause rashes and photosensitivity. Treatment involves stopping B6.

Copper deficiency/Zinc toxicity: copper deficiency most often related to prior bariatric surgery. Can be caused by high zinc intake as this blocks absorption of copper by enterocytes (ex. in excessive denture cream use, which can contain a lot of Zinc). Typically leads to a myelopathy but can also cause a peripheral neuropathy or myeloneuropathy. Test for serum copper or serum ceruloplasmin levels. Management focuses on removing sources of excess zinc and replacing copper (no set guidelines for doing this, some sources recommend IV for several days followed by oral repletion, others recommend oral repletion only).

Vitamin E deficiency: Fat soluble vitamin with antioxidant properties. Deficiency results from poor fat absorption and poor intake is rarely a cause. May take years of depletion before symptoms result. Can cause a spinocerebellar syndrome or a large fiber neuropathy. Replete with 50-500 mg/day and follow serum alpha-tocopherol levels.

Vitamin	Confirmatory Testing	Dosage/Route	Length of Treatment/ Comments	Comments
Vitamin B_{12}	Serum vitamin B_{12} (methylmalonic acid)	1 mg IM/subcutaneous weekly for 1 month, then monthly	Lifelong unless a reversible cause is identified	Investigate for concomitant folate deficiency
Copper	Serum copper (ceruloplasmin, urine copper)	Elemental copper (oral): 8 mg/d for 1 week, 6 mg/d for 1 week, 4 mg/d for 1 week, 2 mg/d thereafter	Lifelong unless a reversible cause is identified	Investigate for zinc excess
Vitamin E	Serum vitamin E	Vitamin E (oral/IM): 200 mg/d to 200 mg/kg/d depending on severity and cause	Lifelong unless a reversible cause is identified	
Vitamin B_6	Vitamin B_6	50 mg oral daily	Only necessary in setting of isoniazid or prolonged hydralazine treatment	High-dose vitamin B_6 supplementation causes sensory neuropathy or sensory ganglionopathy

IM = intramuscular.
[a] Updated from Staff NP, Windebank AJ, Continuum (Minneap Minn).[1] © 2014 American Academy of Neurology. LEARNING IN NEUROLOGY

From Peripheral Neuropathies Due to Vitamin and Mineral Deficiencies, Toxins, and Medications. Staff, Nathan P. CONTINUUM: Lifelong Learning in Neurology26(5):1280-1298, October 2020.

CHEMOTHERAPY INDUCED NEUROPATHIES (CIPN)

Please also see Neuro-Oncology section with more information on chemotherapy-induced peripheral neuropathies.

NEUROMUSCULAR

HEREDITARY

Overview: >100 genes now implicated in causing hereditary neuropathies, though CMT1 is most common. Can see onset in infancy to late in adult life. Typically affect just the PNS although some mutations can lead to CNS involvement. Can broadly classify into predominantly motor-sensory or predominantly sensory-autonomic.

Motor-Sensory

Charcot-Marie-Tooth Disease (CMT): CMT is a spectrum of disorders caused by mutations in genes involved with myelin or axons. Majority of cases are caused by mutations in *PMP22, MPZ, GJB1 and MFN2*. Commonly presents with distal weakness (foot drop). Less prominent sensory loss. Look for pes cavus or hammer toes on exam. EMG typically with demyelinating features with uniform slowing into demyelinating range on NCS without conduction block or temporal dispersion. CMT2 will show axonal pattern of injury.

Can CMT patients get chemo? CMT patients are considered more susceptible to injury when exposed to neurotoxic agents. For chemotherapy, case series have shown that vincristine can cause an acute worsening in CMT patients and is considered a high risk medication in CMT patients and is contraindicated. The platin agents are also best avoided. A number of other medications are thought to be a moderate risk and can be found on the CMT UpToDate page.

Can CMT patients get regional chemo? Theoretical concern due to nerve damage from local anesthetics, although case series have not shown harm from these agents.

Hereditary neuropathy with liability to pressure palsy (HNPP): episodic demyelinating neuropathy with autosomal dominant inheritance. Deletion in *PMP22*. Frequent isolated nerve palsies in sites of compression that typically resolve. Can also get atypical polyneuropathy. Best treatment is to find ways to avoid nerve compression (avoid crossed legs, leaning on elbows, sleeping with elbow pads). Not clear if HNPP patients benefit from carpal tunnel release surgery.

Sensory-Autonomic

Hereditary sensory and autonomic neuropathies (HSAN): occur much less frequently than the above etiologies. Large myelinated/unmyelinated fibers affected. HSAN1 is most common type, caused by degeneration of dorsal root ganglion and eventually motor neurons. Genetically heterogenous and caused by mutations in 5 different genes. Mainly autosomal dominant.

Common types of inherited neuropathies			
Disease	**Gene**	**Inheritance Pattern**	**Clinical features**
Motor-Sensory			
CMT1A	Duplication of *PMP22*	Autosomal dominant	1-2nd decade...foot drop...normal life expectancy...typically maintain ability to walk lifelong
CMT1B	Point mutation of *MPZ*	Autosomal dominant	Several phenotypes...early onset severe demyelinating neuropathy or late onset axonal neuropathy
CMT2A	*MFN2* mutation	Autosomal dominant	Similar to CMT1, but with more prominent sensory symptoms...see **axonal injury** not demyelination

CMTX1	*GJB1* mutation	X-linked dominant	Boys worse off, present with weakness in infancy...can see deafness...stroke like episodes reported...see demyelination and axonal loss
HHNP	1.5 mb deletion of *PMP22*	Autosomal dominant	Frequent pressure palsies...2nd decade...median, peroneal, ulnar, brachial plexus, radial nerve frequently involved...treat by avoiding trauma + compression
Sensory-Autonomic			
HSAN1	*SPTLC1, SPTLC2, ATL1, DNMT1, ATL3 mutations*	Mainly autosomal dominant	Early adulthood onset...distal sensory loss early then motor wasting...actually don't have much autonomic symptoms...

IDIOPATHIC

Overview: Almost 20-40% of patients may have no identifiable cause for their polyneuropathy despite appropriate evaluation. Most cases like this will be in older individuals (>50 years) with a slowly progressive sensory neuropathy. Strength typically preserved. Typical EMG shows axonal features. Label of Chronic Idiopathic Axonal Polyneuropathy (CIAP) has been generated. Can consider genetic testing and discussing with genetic counselor if patient would be a candidate for any experimental genetic testing (some studies/companies offer genetic testing for free, so it's worth inquiring).

Myasthenia Gravis

Clinical Manifestations: acquired autoimmune disorder with antibodies against acetylcholine receptor. 2:3 M:F with bimodal peaks – female 20s, male 50s. 20% have bulbar symptoms, 50% with ocular symptoms, 5% with fluctuating muscle weakness only. In patients initially presenting with ocular myasthenia more than half will develop generalized myasthenia in 2 years.
Exam hints: difficulty with sustained upgaze, curtaining, Cogan's lid twitch, decreased single breath count

Workup:
1) Serologic Ab testing: Ach-R Ab (binding > blocking > modulating) and MuSK-Ab; 90% sensitive in generalized disease, Ach-R Ab present in 50% of patients with ocular myasthenia; 99% specific.
- In all pts, 85% ACh-R Ab, 8% MuSK, 1% LRP4, 6% seronegative

2) EMG/NCS: Repetitive nerve stimulation or single fiber EMG (most sensitive)
3) CT or MRI Chest for thymoma: less common in MuSK or LPR4 pts
4) Less commonly used: ice-pack test (assess ptosis after 2 minutes of ice pack on eyelids)

Treatment:
1) Symptomatic therapy:
- ACh-E inhibitors: pyridostigmine (Mestinon) Start 30 PO TID, increase to 60-120 mg q4-6 hrs (maintenance), can increase to 120 mg q3 hrs (maximum). Usually helps more with limb weakness than ocular weakness.
- Long acting Mestinon (timespan) can be given QHS for pts with nocturnal or early morning weakness.

- Glycopyrrolate 1mg with each dose to combat cholinergic side effects if needed
- Take with food to mitigate GI ASEs

2) Chronic immunosuppression: indicated if symptomatic despite pyridostigmine or severe disease

- Glucocorticoids: used initially, high doses (>30 mg) will worsen MG initially
- Steroid-sparing agents: azathioprine, mycophenolate > MTX, tacrolimus, cyclosporine
- IVIG/PLEX: can bridge with monthly therapy while steroid sparing agents take effect or in some patients used as maintenance
- Rituximab: used in MuSK+ refractory to other treatment
- Eculizumab (Solaris): IV infusion q1-2 weeks; requires meningococcus vaccine (both ACYW135 and serogroup B)
- Efgartigimod alfa (Vyvgart): neonatal Fc receptor blocker recently approved for MG

3) Thymectomy: Indicated for all patients with thymoma. Also beneficial for all adult patients under the age of 65 with thymus gland (reduces steroid use, frequency of flares, and functional limitations over 3 years following)

4) Treatment of acute flares (see below)

5) Avoid medications that can exacerbate myasthenia - see chart below

6)Other recommendations: yearly inactivated flu vaccine, pneumococcal vaccine, AVOID/weigh risk of live attenuated vaccines with risk of immunosuppression

MEDICATIONS THAT MAY EXACERBATE MYASTHENIA

Antibiotics: Aminoglycosides (gentamicin, streptomycin others) Peptide antibodies (polymixin B, Colistin) Tetracyclines (tetracycline, doxycycline, others) Erythromycin Clindamycin Ciprofloxacin (fluroquinolones) Ampicillin	Antiarrhythmics (Quinidine, Procainamide, Lidocaine) Neuromuscular Junction Blockers (vecuronium, pancuronium, others) Quinine Steroids Thyroid Hormones (thyroxine, levothyroxine, others) Beta Blockers (propranolol, timolol, others) Phenytoin Anecdotal: Verapamil, Trimethaphan, Trimethadione, Li, chlorpromazine, Neurontin

Myasthenic Crisis:

-Symptoms include facial diparesis, ptosis, neck extensor weakness, nasal voice, hypotonic and weak

-May be precipitated by medication non-compliance, infections, exacerbating drugs

-Before admitting patient, assess respiratory status with vital capacity and NIF. Just like in GBS if VC below 15 cc/kg and NIF below 30 cm H2O (or close to these numbers) you should be discussing admission to NICU for close monitoring and early intubation. Anybody with concern for respiratory status should be in INCU at very least. If initial NIF/VC off baseline can trend q 2-4 hours until stable.

- Note 1: Be aware of poor seal due to facial weakness, may give falsy low VC/NIF reading
- Note 2: ABG and pulse ox changes will lag behind hypoventilation. Hypercapnea is a very late finding in the context of an acute repiratory dysfunction like a myasthenic crisis

Treatment of flares

- Acute treatment with IVIg and/or plasma exchange, plus initiation of acetylcholinesterase inhibitors (exception below).

- Increase in steroids may acutely worsen symptoms in 1/3 of patients, but should be considered.
- Existing anticholinesterase medications should be stopped while patient is on ventilator, due to increased secretions affecting weaning. Restart at ½ dose 1 day prior to extubation.

Myopathies

Immune mediated myopathies

Dermatomyositis

Clinical features: subacute proximal muscle weakness with skin rash (generally in photosensitive areas). Can see heliotrope rash with edema of upper eyelids, rash on extensor surfaces of joints, anterior chest (V sign), back and shoudlers (shawl sign). Patients can have rash without weakness...can see involvement of cardiac, pulmonary, GI systems, joints. Can present in children and adults

Diagnosis:

- **Creatinine Kinase** elevated into thousands, although can be normal and CK level may not reflect disease severity
- **EMG** with generally normal NCS (although low amplitude motor responses can be seen with severe disease). EMG will show abnormal spontaneous activity and myopathic changes
- **Antibody testing:** there are 5 known dermatomyositis specific autoantibodies that have specific clinical phenotypes and prognostic markers
  - Mi-2 – classic skin rash, moderate muscle involvement, favorable treatment response
  - TIF-1gamma – strong cancer association, severe rash, variable muscle involvement
  - NXP-2 – increased malignancy risk, subq calcifications, peripheral edema
  - MDA-5 – severe rash, minimal muscle involvement, interstitial lung disease
  - SAE- classic rash with mild muscle involvement, dysphagia
- **Pathology** with CD4+ T cells in the perimysium and perivascular regions, can see perifascicular atrophy and evidence of active muscle fiber necrosis and regeneration

Cancer screening:

- Majority of malignancies are found in first 3 years after diagnosis of myositis.
- Most often see adenocarcinomas of cervix, lung, ovaries, pancreas, bladder, stomach.
- Aggressive cancer screening should include chest, abdomen, pelvis CT scans, age appropriate screening with mammogram, colonoscopy, gyn exam if indicated.

A word about Polymyositis: historically was marked by proximal muscle weakness + elevated CK, myopathic EMG, endomysial inflammation with C8+ T cells on biopsy. However, over the years studies have shown that many patients with polymyositis actually have another etiology on further evaluation – IBM, immune mediated necrotizing myopathy etc. Due to this we will not extensively discuss this entity here.

Immune mediated necrotizing myopathy (IMNM)

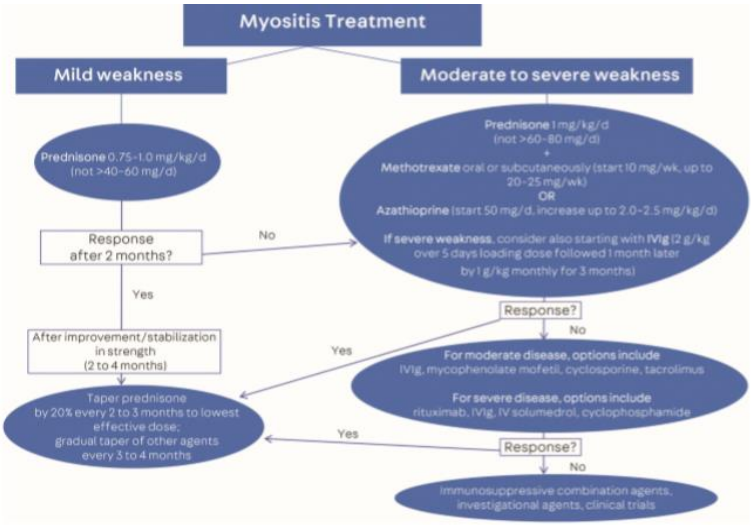
Clinical features: severe proximal muscle weakness with rare extramuscular involvement and myofiber necrosis with lack of inflammatory infiltrates on path...some cases may be related to statin exposure, but this is not always the case.

Diagnosis:

- **Creatinine Kinase**: typically markedly elevated the several thousands (mean is around 4700). CK can be followed during medication weans to detect return of disease activity
- **EMG** with myopathic motor units and evidence of irritable muscle fibers with high levels of spontaneous activity

- **Antibody testing:** two main auto-antibodies are associated with IMNM -- SRP and HMG-CoA reductase. These account for two thirds, the other 1/3 is antibody negative
  - SRP – reported in 5% of cases, have very aggressive disease that may not respond well to steroids. Does not have association with cancer.
  - HMG-COA reductase – first described with statin exposure, but can happen without. Has weak association with cancer.
  - Autoantibody negative: higher risk of cancer, warrants aggressive screening.
- **Pathology**: necrotic fibers seen with very little lymphocytic infiltrates. Do not see the perifascicular atrophy seen in dermatomyositis

Treatment principles: *From treatment pathway for Immune mediated Myopathies, Continuum December 2019 issue:*



Caveat

-Prednisone has limited long term usage given side effects and second agent is typically started early in course in efforts to wean down steroids

Inclusion body myositis

Clinical Features: slowly progressive weakness presenting after age 45. Quads and finger flexors involved initially. Has both an autoimmune component and degenerative component. Treatment is limited but disease progression is generally slow. Falls are main cause of morbidity and aspiration risk needs to be monitored. Most often is sporadic, can see similar disease from *VCP* mutations (can also cause FTD/Paget disease of bone).

Diagnosis:

- **Creatinine Kinase**: Typically modestly elevated with levels less than 1500.
- **EMG**: abnormal spontaneous activity with recruitment pattern that can vary from reduced to increased – reflecting a mixed neurogenic/myopathic process. Can also see a concurrent sensory axonal polyneuropathy.
- **Antibody testing**: serum autoantibody against anti-5'-nucleotidase, cytosolic IA (NT5C1A) identified in 40-60% of patients with sporadic IBM. Not specific however, can be present with other autoimmune diseases.

- **Pathology**: Biopsy with features of active myopathy with variations in fiber size, hypertrophic fibers, small angulated fibers. Can see fatty replacement. Endomysial inflammation present but can be missed. Rimmed vacuoles that we typically associate with disease are easy to miss.

Treatment: No disease modifying therapy currently. Most patients will lose ability to walk in 10-20 years. Dysphagia can occur. Sporadic IBM does not lead to decreased survival if falls/aspiration can be prevented.

Toxic myopathies

There are a wide range of toxic myopathies with a wide range of presentations. Generally, presentation includes a subacute proximal weakness with muscle pain. Recognizing the link between the myopathy and drug is important as cessation of the offending drug can often lead to recovery. Only one common cause will be presented here.

Statins

Mechanism: unclear, may be due to destabilized muscle membrane from reduced cholesterol and impaired energy production from reduction in downstream HMG-CoA reductase pathway.

Clinical features: asymptomatic CK elevation occurs in 5% of patients, myalgias/cramps 20% (may not be statin related though – statin related myalgia is generally large proximal muscles). Severe myopathy occurs in less than 1% of patients. Also associated with IMNM (above). Risk increased with concurrent medication that inhibits cytochrome P450 pathway (AVOID GRAPEFRUIT JUICE). Gemfibrozil and cyclosporine are highest risk. Symptoms typically occur in first 6 month on medication.

How to tell if myalgias are statin related?

See Statin-Associated Muscle Symptoms Clinical Index (to right) for one clinical guide.

Table 2 Proposed statin myalgia clinical index score

Clinical symptoms (new or increased unexplained muscle symptoms)	
Regional distribution/pattern	
Symmetric hip flexors/thigh aches	3
Symmetric calf aches	2
Symmetric upper proximal aches	2
Non-specific asymmetric, intermittent	1
Temporal pattern	
Symptoms onset <4 weeks	3
Symptoms onset <4 weeks	3
Symptoms onset 4–12 weeks	2
Symptoms onset >12 weeks	1
Dechallenge	
Improves upon withdrawal (<2 weeks)	2
Improves upon withdrawal (2–4 weeks)	1
Does not improve upon withdrawal (>4 weeks)	0
Challenge	
Same symptoms reoccur upon rechallenge <4 weeks	3
Same symptoms reoccur upon rechallenge 4–12 weeks	1
Statin myalgia clinical index score	
Probable	9–11
Possible	7–8
Unlikely	<7

When should I stop the statin?

- If your patient has objective weakness or rhabdo, stop immediately.
- CK values will usually normalize in 1 week – 2 months, clinical symptoms may lag behind

How to differentiate between statin induced myopathy and immune mediated necrotizing myopathy?

- CK levels can be very high in both cases
- EMG can show an irritating myopathy in both cases
- HMG-CoA autoantibodies **should not** be present in cases of run of the mill statin induced myopathy (the antibodies are specific for IMNM)
- Useful indicator is what the CK does after statin cessation: in case of statin induced myopathy you can expect the CK to improve after a couple weeks. In IMNM the CK will not normalize in the absence of starting immunotherapy. If the HMG-CoA reductase is negative you can perform a muscle biopsy if there is clinical ambiguity – IMNM can show complement membrane attack complex on the sacrcolemmas of non-necrotic myofibers – although you may not see this on biopsy.

NEUROMUSCULAR

Motor Neuron Disease

Clinical manifestations: progressive weakness and muscle atrophy. Slightly higher incidence in men, age of onset around 55-65 years. Typically sporadic. 70% present with limb onset weakness, 25% with bulbar weakness, 5% with trunk/respiratory onset. Median life expectancy is < 3 years.

Diagnosis: El Escorial criteria used to stratify certainty of diagnosis based on presence of UMN and LMN in different segments of body + confirmation on EMG

- **EMG** will show evidence of ongoing denervation (spontaneous activity) and renervation (large amplitude/duration motor unit action potentials. NCS may show normal conduction down sensory and motor nerves. CMAP may be reduced with severely affected muscles
    - **The best-case scenario for a presentation of progressive, painless lower motor neuron weakness if that the patient has multifocal motor neuropathy (MMN)** which on the EMG will typically show conduction block without abnormalities in the sensory nerves. Typically responds to IVIG. Differentiate from progressive muscular atrophy which a is LMN-only form of ALS that does not respond to IVIg
- **Likely will get pan MRI of the neuroaxis +/- LP** given implication of the ALS diagnosis and need to exclude other etiologies

Management:

- Refer to ALS center - patients benefit from multidisciplinary care and access to clinical trials
- Average time from symptom onset to diagnosis is 18 months, median life expectancy <3 years (20% survive 5-10 yrs)
    - Reduced survival seen in older patients, dysphagia, respiratory dysfunction
- Significant overlap with FTD (20-50% of ALS patients have both diseases) d/t similar pathologic TDP-43 cytoplasmic inclusions
- Riluzole is the only effective therapy at prolonging life (median prolongation 3 months)
- Edaravone (Radicava) showed delayed disease progression over 24 weeks in subset patients with early/mild disease (duration<2 yrs, VC preserved). No effect on survival. Very bothersome to administer as it requires IV dosing q 2 weeks and placement of durable IV access. Need to discuss with pt/family if this is worth the risk/time involved.
- Tofersen is approved for the treatment of ALS patients with SOD1 mutations

Mimickers of ALS

NEUROMUSCULAR

Panel 2: Differential diagnosis of ALS and appropriate investigations

Disorders of motor neurons
- Spinal muscular atrophy (SMN gene deletion assay)
- X-linked spinobulbar muscular atrophy (Kennedy's disease; increased CAG repeats in DNA from blood)
- Poliomyelitis or post-polio syndrome (history, NCS, electromyography)
- Hexosaminidase A deficiency (white-cell enzyme testing)

Disorders of motor nerves
- Multifocal motor neuropathy (NCS, electromyography, ganglioside GM1 antibodies)
- Chronic inflammatory demyelinating neuropathy (NCS, lumbar puncture)
- Cramp-fasciculation syndrome (NCS, electromyography)
- Neuromyotonia (antibodies to voltage-gated potassium channels)
- Hereditary spastic paraparesis plus (gene mutation testing)
- Hereditary motor neuropathy with pyramidal features
- Radiculoplexopathy (NCS, electromyography, MRI)
- Paraneoplastic syndrome (serum markers, imaging, bone marrow biopsy sample)
- Heavy metal poisoning (urine or blood screens)
- Mononeuritis multiplex (NCS, electromyography, vasculitic screen, serology)

Disorders of neuromuscular junction
- Myasthenia gravis (acetylcholine receptor antibodies, MuSK antibodies, repetitive stimulation, single-fibre electromyography)
- Lambert-Eaton myasthenic syndrome (repetitive stimulation)

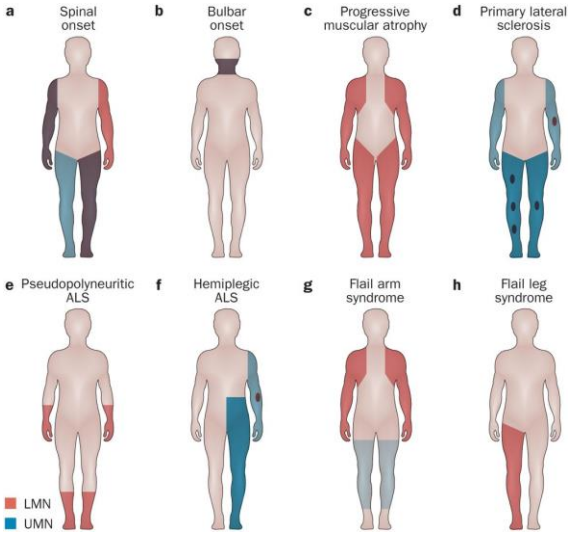
Structural CNS and spinal lesions
- Syringomyelia or syringobulbia (MRI)
- Tabes dorsalis (syphilis serology)
- Multiple sclerosis (MRI, oligoclonal bands, evoked responses)
- Monomelic spinal muscular atrophy (Hirayama's disease; electromyography, MRI)
- Lyme disease (Lyme serology)
- Human T-lymphotropic virus-1 (HIV)

Myopathy
- Inclusion body myositis (electromyography, CK, muscle biopsy sample)
- Polymyositis (electromyography, CK, muscle biopsy sample, autoimmune screens)
- Dermatomyositis (electromyography, CK, skin, and muscle biopsy sample)
- Polyglucosan body disease (NCS, electromyography, muscle or nerve biopsy sample)

Endocrine
- Thyrotoxicosis (thyroid function tests, electromyography, muscle biopsy sample)
- Hyperparathyroidism (calcium ion and parathyroid testing)
- Subacute combined degeneration (vitamin B_{12} concentrations)
- Coeliac disease (serum testing, bowel biopsy sample)

ALS=amyotrophic lateral sclerosis. CK=creatine kinase. NCS=nerve conduction studies. MuSK=muscle specific tyrosine kinase.

ALS Variants



NEURO-ONC

TUMORS OF THE BRAIN:

INTRACRANIAL METS:

- Parenchymal mets from other cancers (breast, lung, melanoma) are 10x more common than primary brain tumors.
- 1+ ring-enhancing lesions seen on MRI w/ and w/o contrast, often at grey-white junction
- Mets that most often bleed: melanoma, choriocarcinoma, renal cell carcinoma
- Workup: CT Chest/Abd/Pelvis to look for a mass, if high suspicion and these are negative, consider PET/CT.
- Treatment: surgery for up to three accessible metastases, followed by focal or whole-brain radiation (for multiple mets).WBRT reduces local recurrence but is associated with cognitive morbidity

LEPTOMENINGEAL METS:

- AKA carcinomatous meningitis
- Think of this in a patient with headache, n/v, cranial nerve involvement, confusion and otherwise concern for cancer
- Primaries: breast, lung, hematologic ca, and melanoma are most common.
- Imaging: MRI Brain w/ and w/o contrast may show leptomeningeal enhancement, also possible to see hydrocephalus
- Definitive dx w/ LP for flow and cyto. May require serial LPs given low sensitivity
- Treatment: focal or whole-brain radiation (symptomatic relief without mortality benefit), intrathecal chemotherapy, systemic therapy (cytotoxic or immunotherapy) targeted at primary tumor (NSCLC, breast, lymphoma). Proton therapy spares cord
- Clinical Pearl: **Numb Chin Sign—**if a pt w/ known cancer has a numb chin, think of leptomeningeal disease or involvement of the mental nerve.

PRIMARY BRAIN TUMORS:

- Can arise from any cell line, however, most commonly seen are gliomas and meningiomas.
- **Meningiomas:**
    - Risk factors: **age**, radiation, genetic (NF2)
    - Presenting symptoms: seizures, increased ICP, any symptoms associated with compression of surrounding structures.
    - Dural-based, homogeneously enhancing mass on MRI. More malignant masses (grade 2 or 3I) may have necrosis and peri-tumoral edema
    - Tx: neurosurgical intervention. If inoperable, can consider stereotactic radiation
    - If found incidentally and asymptomatic, can monitor with serial imaging over time.
- **Gliomas:**
    - Low grade gliomas= Grade 1-2, high grade gliomas= grade 3-4. Grade 4 is **glioblastoma multiforme (GBM)** and by definition is IDH wild-type
    - Low grade: imaging will show T2/FLAIR hyperintense lesions with minimal contrast enhancement. Likely to be IDH-mutant. Tx: surgical resection
    - High grade/Glioblastoma: imaging will show contrast-enhancing, heterogeneous mass, central necrosis. Classic finding is “butterfly glioma” across the corpus callosum but also presents in other locations. IDH-mutant and MGMT methylation have better prognosis
    - Treatment: maximal surgical resection, radiation, and temazolamide (more effective with MGMT methylation). Recurrence: bevacizumab (VEGF inhibitor)
- **Primary CNS Lymphoma:**
    - Primarily diffuse-large B cell lymphomas (DLBCLs)
    - Presentation: symptoms over weeks to months related to anatomic structures

affected. Can include ocular symptoms (similar to uveitis)
- Diagnosis: MRI with homogenously enhancing, diffusion-restricting lesions, either solitary or multifocal. LP x 3 for flow and cyto (though this will not always yield a diagnosis). Ophtho exam. If negative but still have high suspicion, biopsy.
  - Exquisitely sensitive to steroids, so if planning to biopsy, **HOLD OFF ON STEROIDS PRIOR TO BIOPSY** as this may affect the yield of the procedure.
- Treatment: chemotherapy (high-dose methotrexate, rituximab, temozolomide). Can consider whole brain radiation at recurrence but with cognitive side effects. Biopsy rather than debulking surgery recommended.
- Relapses common: consider whole-body PET as can have systemic relapse
- **Intravascular lymphoma:** rare. Proliferation of lymphoma cells within lumina of small blood vessels. Causes strokes and skin changes. Diagnosis with deep skin or brain biopsy

TUMORS OF THE SPINAL CORD

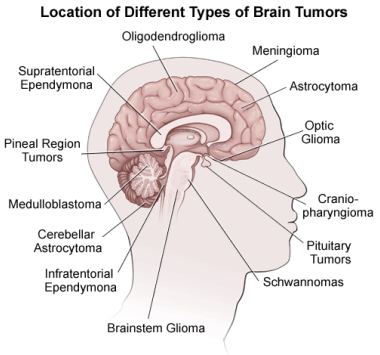
- Symptoms: think of this in patients with back pain and subacute myelopathy. Can also see vertebral fx.
- Intramedullary (inside the SC)- Types: Ependymoma, astrocytoma, glioblastoma, lymphoma, intramedullary mets. Extramedullary (outside the SC)- dural mets, meningiomas.
- Spinal metastases are likely the result of breast, lung, prostate, thyroid, or renal cell cancers
- Spinal cord compression from metastases is a surgical emergency: if suspected, start high-dose steroids, and consult neurosurgery/radiation oncology

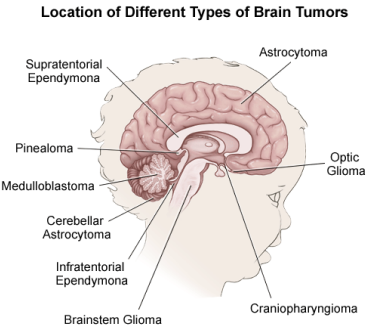
OTHER TUMORS TO KNOW:

- CN: Vestibular Schwannoma. MRI w/ gad is the best diagnostic tool. If bilateral, think NF2.
- PNS: Rare. schwannomas, neurofibromas, MPNST.
- NF1: optic gliomas, neurofibromas.
- NF2: bilateral vestibular schwannomas, meningiomas.
- Tuberous Sclerosis: Cortical tubers, SEGA

A SUMMARY OF TUMORS BY AGE AND LOCATION

	SUPRATENTORIAL	VENTRICULAR	CEREBELLAR	PINEAL	SELLAR	SPINAL	PERIPHERAL	MISC.
ADULTS	- Oligodendroglioma - Diffuse astrocytoma - Anaplastic astrocytoma - GBM	- Ependymoma - Subependymoma - ** Colloid Cysts (not a tumor!)	- Hemangioblastoma	- Pineocytoma	- Pituitary Adenoma	- Ependymoma (again)	- Schwannoma - Neurofibroma - Malignant Peripheral Nerve Sheath Tumor (MPNST)	- Meningioma - CNS Lymphoma
KIDS	- Pleomorphic xanthoastrocytoma - Neuronal and Mixed Neuronal-Glial Tumors (Gangliocytoma/Ganglioglioma/DNET)	- Central Neurocytoma - Ependymoma - Choroid Plexus Papilloma - Medulloblastoma - SEGA	- Pilocytic Astrocytoma	- Pineal Germinoma	- Craniopharyngioma - Hypothalamic Hamartoma - ***Rathke's cleft cyst (not a tumor!)	- Chordoma - Ependymoma (again)		- Retinoblastoma - Neuroblastoma





NEURO-ONCOLOGIC EMERGENCIES (INPATIENT/ED)

Ddx for AMS in the Neuro-Onc patient:
- Neoplastic (parenchymal, leptomeningeal, spinal)
- Infectious (non-CNS vs. CNS infection)
- Medications (pain meds, sedatives, anti-depressants)
- Complications of oncologic treatments
- Metabolic/Nutritional abnormalities (think Wernicke's, hyperammonemia, LFTs, Ca)
- Non-convulsive status epilepticus

Seizures: occur in 20-70% pts w/ intracranial tumors. Up to 1/3 will have recurrent seizures. Low grade glial tumors (60-85%), high grade glial tumors (20-40%), meningiomas (~38%)> PCNSL (~17%), brain mets (15-20%).

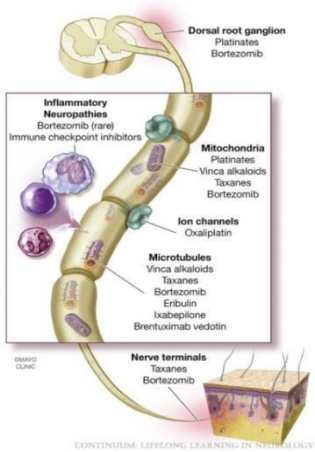
NEUROTOXICITIES OF SYSTEMIC CHEMOTHERAPY

Chemotherapy	Side Effect	Risk Factor/Treatment
Cytarabine	Cerebellar syndrome	Old age, renal failure, and high dose
Methotrexate	Delayed leukoencephalopathy	High dose, older age, whole brain radiation
Methotrexate	Acute encephalopathy	
Methotrexate	Seizures	Treat with anti-seizure meds
Ifosfamide	Acute encephalopathy	Treat with methylene blue
Ifosfamide	Seizures	Treat with anti-seizure meds
Vincristine	Sensory and motor neuropathy	
Platinums (oxaliplatin), Taxol	Sensory neuropathy	
Bevacizumab	PRES, ICH/stroke	
Intrathecal Chemotherapy	Aseptic Meningitis	Pre-treat with intrathecal hydrocortisone
Cyclosporine/Tacrolimus	PRES	
5-FU	Cerebellar syndrome	
Busulfan	Seizures	Treat with anti-seizure meds
Bortezomib	PRES	
L-asparaginase	VST	

(Adapted from *Clinical Neurology and Neuroanatomy: A Localization-Based Approach* by Aaron Berkowitz, M.D. and Dr. Pruitt's Neuro-Oncology JAR Bootcamp lectures)

CHEMOTHERAPY INDUCED NEUROPATHIES

- **Most common associated chemotherapeutics:** platinum compounds (cisplatin, oxaliplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinca alkaloids (vincristine, vindesine, vinblastine)
- **Most common form** is a painful and length-dependent, predominantly sensory, and symmetric peripheral neuropathy with paresthesia in the hands and feet
- **Treatment:** usually reversible with removal of offending agent. Can symptomatically treat neuropathy with SNRIs (proven benefit in RCT), gabapentinoids, or TCAs. Longitudinal EMG/NCS can be helpful to monitor improvement
    - *Coasting:* observed after treatment with platinum agents and is characterized by peripheral neuropathy that worsens several months after chemotherapy discontinuation.



Chemotherapy	Type of Neuropathy	Pathology	Symptoms	Prognosis and Outcome[a]
Platinum compounds				
Cisplatin	Large fiber, sensory	Dorsal root ganglion, mitochondrial damage	Numbness and paresthesia, loss of deep tendon reflexes	Reversible within months of drug cessation
Oxaliplatin	Large fiber, sensory, acute and chronic	Dorsal root ganglion, sodium channelopathy	Oropharyngeal allodynia and paresthesia (acute and infusion related)	Reversible within months of drug cessation[b]
Vinca alkaloids (vincristine, vinblastine, vindesine)	Small fiber, mixed sensorimotor, autonomic involvement	Dorsal root ganglion, terminal nerve fibers, microtubule injury	Numbness and paresthesia, weakness, cranial neuropathies, gastrointestinal motility dysfunction, hypotension	Reversible within months of drug cessation
Taxanes (paclitaxel, docetaxel)	Large and small fiber, mixed sensorimotor	Dorsal root ganglion, terminal nerve fibers, axonal transport, mitochondrial and microtubule injury	Numbness and painful paresthesia, myalgia, arthralgia	Reversible within months of drug cessation
Bortezomib	Small fiber, sensory, axonal	Damage to mitochondria, endoplasmic reticulum, DNA, and microtubules	Numbness and painful paresthesia	Reversible after dose reduction and drug cessation
Thalidomide	Small and large fiber, mixed sensorimotor	Dorsal root ganglion, antiangiogenesis, axonal damage, dysregulation of neurotrophin activity	Distal painful paresthesia, myalgia	Reversible after drug cessation
Suramin	Mixed sensorimotor, axonal and demyelinating	Dorsal root ganglion	Distal painful paresthesia	Reversible after drug cessation

DNA = deoxyribonucleic acid.
[a] Symptoms are usually reversible with dose reduction or drug cessation, but recovery can be incomplete.
[b] Acute, infusion-associated form of neuropathy typically subsides within hours to a few days.

From *Continuum*, December 2020

CHEMOTHERAPY-ASSOCIATED CNS EFFECTS

Acute encephalopathy: most commonly associated with alyklating agent (i.e. cyclophosphamide), anti-metabolites (i.e. methotrexate), anti-hormonals, and vinca alkaloids.

- Acute encephalopathy hours-days after chemotherapy initiation
- MRI usually without changes
- Complete recovery after cessation of offending agent
- May be associated with aseptic meningitis, especially after intrathecal administration. Tx: steroids

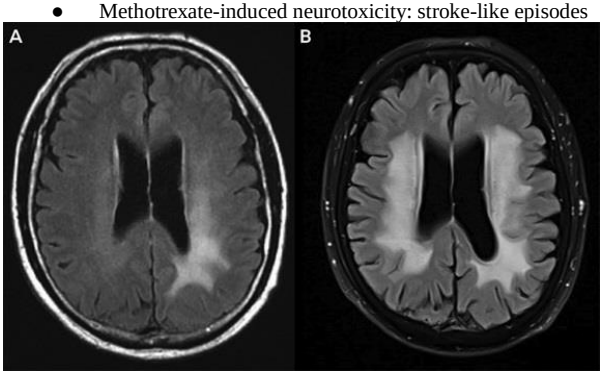
PRES: Associated with a variety of chemotherapies, usually hours-days after initiation. Reversible after removal of offending agent

Cerebellar toxicity: most commonly associated with high-dose cytosine arabinosid (up to 10-20%) but also with cyclopsorine, 5-FU, and vincristine. Although most recover, may have permanent cerebellar dysfunction. MRI with cerebellar atrophy.

Cognitive changes: associated with cisplatin, corticosteroids, 5-FU, methotrexate, and increased prevalence with brain radiation. Presents as impairment with memory function and multitasking. Can be either transient or permanent. Can consider donepezil and neurostimulants

Leukoencephalopathy: usually delayed-onset and irreversible. Most commonly implicated agents that cause delayed leukoencephalopathy are methotrexate, cytosine arabinoside, fludarabine, ifosfamide, vincristine, and carmustine.

- Presentation: cognitive and personality changes, motor and coordination deficits, and urinary incontinence developing over months to years
- Diagnosis: MRI with diffuse and confluent subcortical and periventricular T2/FLAIR hyperintensities, which may be associated with communicating hydrocephalus, and progressive cerebral atrophy
- Methotrexate-induced neurotoxicity: stroke-like episodes



From *Continuum*, December 2020

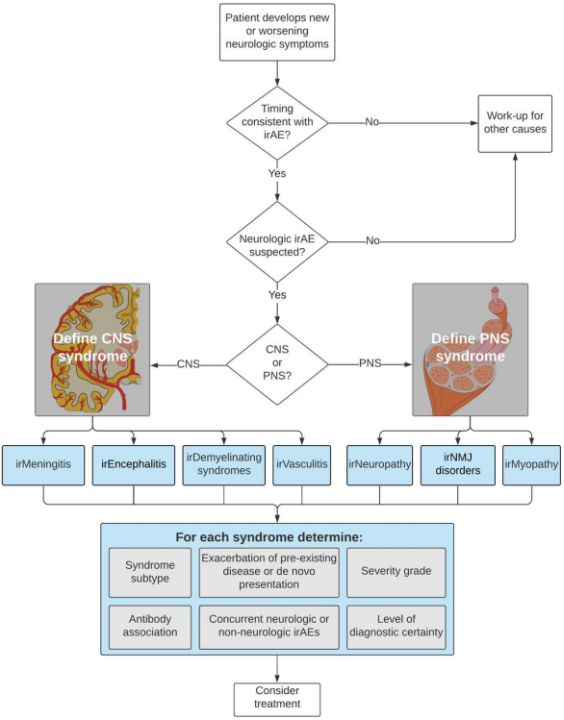
Neurologic Complications of Immune-Checkpoint Inhibitors (irAE0:

CTLA-4 and **PD-1** are negative regulators of T-cell function, and have been the target of a variety of novel cancer immunotherapies. They have been associated with a variety of neurological symptoms.

Presentation:

- PNS complications include GBS, myasthenia gravis, and myositis.
- CNS complications include meningitis, encephalitis, demyelination, and vasculitis
- Symptoms typically **start within 3 months**, and is very unusual to start > 1 year from ICI initiation

Diagnosis: ensure timing is appropriate. Clinical diagnosis after excluding alternative etiologies.



From *Consensus disease definitions for neurologic immune-related adverse events of immune checkpoint inhibitors*

Treatment: discontinuation of ICI, corticosteroids, consider IVIg. **ASCO guidelines have disease-specific treatments and are a good resource if irAE are suspected**

- Partial or complete recovery ~73% cases
- Duration 4-9 weeks
- Safety of resuming ICIs is unclear

Neurologic Complications of CAR T- Cell Therapy:

Referred to as immune effector cell-mediated neurotoxicity syndrome (ICANS). Neurotoxicity occurs in 60-80% of patients. Symptoms range from mild encephalopathy to behavioral changes, aphasia, seizures, and cerebral edema, often associated with cytokine release syndrome. The ICE grading scale can be used to grade severity on a scale of 1-10 (see next page)..Timing is usually 3-10 days after CAR-T initiation, and will resolve within 7-10 days. Treatment includes supportive treatment, steroids, and tocilizumab (esp if there is concurrent CRS).

Cytokine Release Syndrome (CRS)

- Overproduction of inflammatory cytokines caused by overactivation of the immune system
- Symptoms: fever, nausea, fatigue, myalgias, malaise, hypotension, hypoxia, coagulopathy, capillary leak. May lead to HLH/MAS or multiorgan toxicity
- Treatment: tocilizumab. Often associated with ICANS

ICE
• **Orientation:** orientation to year, month, city, hospital: 4 points
• **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points
• **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point
• **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point
• **Attention:** ability to count backwards from 100 by 10: 1 point

ICE: Immune Effector Cell Associated Encephalopathy score

Adopted from Lee et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25(4):625-38

Neurologic Complications of Radiation Therapy:

Characterized with relation to timing of symptoms after radiation therapy::

1. Acute: days-weeks after radiation. Characterized by mental status alteration, fatigue, and worsening of pre-existing neurological symptoms. Symptoms tend to resolve after steroids
2. Early-delayed: weeks to 6 months after radiation. Symptoms include fatigue, nausea, lethargy, and cognitive changes.
3. Chronic: occurring months-years after radiation. Symptoms are typically progressive and irreversible. Symptoms include cognitive decline, leukoencephalopathy, tissue necrosis, vasculopathy, and secondary tumors (esp meningiomas).
    a. Cognitive changes occur in up to 80% of patient receiving radiation, most prominently with whole brain radiation therapy. Treatment: stimulants, donepezil, memantine may help
    b. Leukoencephalopathy: FLAIR hyperintensities within periventricular and deep white matter and global volume loss. Characterized by progressive cognitive decline, gait difficulty, and incontinence (similar to NPH)
    c. Radiation necrosis: may mimic tumor progression. **MRI with perfusion permeability may be helpful to distinguish**
    d. Cerebrovascular disease: infarcts or hemorrhages. SMART (strokelike migraine attacks after radiation therapy) syndrome can be a delayed consequence of radiation. Treatment: steroids + ASMs if needed

Neurologic Complications of Other Non-Neurologic Cancers:

- Ischemic Stroke: Hypercoagulability of malignancy is a frequent diagnosis on the stroke service. See stroke section for management.
    - Ddx may include GVHD arteritis, cerebral emboli, infectious emboli, VZV, intravascular lymphoma, PTLD, radiation-induced vasculopathy leading to strokes.
    - Often ok for AC if Plt count >50K. Consider half-dose if Plt count 25-50K.
- ICH: secondary to thrombocytopenia, hyperleukocytosis
- Epidural spinal cord compression: especially think about this in cancers that cause blastic lesions
- HA/Vomiting/Hydrocephalus: think leptomeningeal disease, which can cause increased ICP
- Cranial nerve involvement: consider leptomeningeal disease
- Nerve root involvement: consider leptomeningeal disease

Misc.:

Not cancer—but there are also **neurologic complications of immunosuppressive medications**:

Tacrolimus can cause PRES, tremor, seizures, leukoencephalopathy, tumefactive MS, CIDP, brachial plexopathy, pseudotumor cerebri, akinetic mutism/CPM, hearing loss, bilateral optic neuropathy, delayed leukoencephalopathy.

NEURO-ONC

PARANEOPLASTIC SYNDROMES

Paraneoplastic antibodies can be divided into cell-surface antibodies (i.e. NMDA) and intracellular (i.e. anti-Hu/ANNA-1). Paraneoplastic syndromes are most commonly associated with intracellular antibodies, and the most common cancer is SCLC, occurring in up to 10% of cases.

Typical presentation includes subacute onset of symptoms, and can often precede the diagnosis of the underlying cancer. Pursue aggressive cancer screening with pan-scan and/or PET scan if suspicious for a paraneoplastic syndrome.

Syndromes	**Diagnostic work-up**	**Associated antibodies and notes**
Limbic encephalitis	-MRI with bilateral or unilateral mesial temporal FLAIR hyperintensities -May have seizures and/or status epilepticus	- NMDA: delta brush on EEG, a/w orofacial dyskinesias and prominent psychiatric features. Often associated with teratoma - GABA-B: often with status epilepticus - LGI-1: associated with faciobrachial dystonic seizures - DPPX: severe weight loss -Others: Anti-Hu (ANNA1), Ma2/Ta, AMPAR, mGluR5, GAD65
Movement disorders	- MRI may have basal ganglia hyperintensities	Anti-Ri/ANNA2: Opsoclonus-myoclonus CRMP5/anti-CV2: chorea with with retinitis and optic neuropathy)
Sleep disorders	Sleep study	- Anti-Ma2: Narcolepsy/cataplexy: - IgLON5: REM sleep behavior disorder, sleep-disordered breathing (rarely paraneoplastic)
Brainstem encephalitis		ANNA-1/Hu, lower brainstem; ANNA-2/Ri , Ma2/Ta, upper brainstem; KLHL11
Subacute cerebellar degeneration	MRI may be normal initially but eventually will have cerebellar atrophy	-Anti-Yo/PCCA1 (breast): poor prognosis -CASPR2: episodic ataxia -Others: ANNA-1/Hu, ANNA-2/Ri, CV2/CRMP5, VGCC P/Q type, Zic-4, PCCA-2, PCCA-Tr/DNER, Ma2/Ta
Encephalomyelitis		-CV2/CRMP5 most common -Others: ANNA1/Hu, Ampiphysin - Progressive encephalomyelitis with rigidity and myoclonus (PERM): GAD65, DPPX, GlyR
Stiff-person syndrome		GAD65, GlyR

Peripheral nerve involvement		Sensory neuronopathy ANNA1/Anti-Hu most common Also CRMP5 CASPR2: Peripheral nerve hyperexcitability (neuromyotonia) Anti-ganglionic acetylcholine receptor antibodies: autonomic neuropathy
Neuromuscular junction		P/Q-type VGCC antibodies: Lambert-Eaton myasthenic syndrome

Note: Chris Brown has a great dotphrase for the above syndromes. Look up .CABPARANEOPLASTIC

Principles of antibody testing:

1. Have a clear hypothesis about what syndrome you are considering - this is imperative to correctly interpret the results of antibody testing
2. Order the panel that covers the syndromes you are considering **in both CSF and serum** if possible. There is no utility in ordering a wider panel than is necessary, and will often be denied by Dr. Price. If there are certain specific tests that aren't on a panel, you can send additional testing through ARUP or Mayo for those specific antibodies (these are ordered as miscellaneous send-outs)
3. If an antibody is positive, it does not mean that the patient has a paraneoplastic etiology of their symptoms, especially if they have low-titers. False-positives are common. Consider if the syndrome fits the antibody, and if there is a question about whether the test is a true-positive, consider repeating testing with a different assay.
4. Consider sending the in-house autoimmune encephalitis panel first, then ARUP if additional antibodies are needed, and finally the full Mayo panels if further antibodies are needed.

Autoimmune Encephalitis Evaluation, CSF (Penn)	**Mayo CSF Paraneoplastic Panel (PAC1/PNEOE) - ordered as "Paraneoplastic autoab eval, CSF"**	**Mayo Serum Paraneoplastic Panel (PAVAL) - ordered as "Paraneoplastic autoab eval, serum"**	**ARUP CSF Paraneoplastic Panel (2010841) - ordered as "Paraneoplastic abs w/ reflex, CSF"**	**ARUP Serum Paraneoplatic panel (2007961) - ordered as "PCCA/ANNA by IFA with reflex"**
AMPA (GluR1, GluR2) Casp2 GABA-B NMDA GAD65 LGI1	Amphiphysin ANNA-1 (Hu) ANNA-2 (Ri) ANNA-3 AGNA-1 CRMP-5 PCA-1 (Yo) PCA-2 PCA-Tr NMDA/LGI1/AMPA/GABA-B/GAD65*	All antibodies in PAC1 plus V-G K+ channel Ca-Channel NMO/AQP4/GAD65/NMDA/GABA-B, AMPA, LGI1*	Purkinje cell antibodies ANNA-1 (Hu) ANNA-2 (Ri) PCA-1 (Yo) TR/DNER	Same as CSF panel

*Mayo will auto-run these antibodies with Serum/CSF paraneoplastic panels if IFA pattern is suggestive of these diseases, but they are not always routinely run

** **Always pair CSF Autoimmune Encephalitis panel with Serum NMDA if clinical suspicion**. For classic paraneoplastic Abs to intracellular antigens (anti-Hu), serum assay more sensitive than CSF though always useful to obtain both Serum & CSF testing

Which panel to send:

Syndrome	**Most common antibodies**	**Test** *For suspected paraneoplastic syndromes discuss with Dr. Lancaster and save CSF for his Lab.*
Encephalomyelitis	ANNA-1 (Hu) ANNA-2 (Ri) ANNA-3 CRMP-5 DPPX (PERM)	ARUP for ANNA1, 2, 3 Misc send out for CRMP-5
Limbic Encephalitis	AMPA (GluR1 GluR2) ANNA-1 (Hu)* ANNA-3 Caspr2** GAD65 GABA-A*** GABA-B LGI-1 NMDA ****	Penn Autoimmune Encephalitis Panel + ARUP Panel for ANNA-1, 2, 3
Cerebellar or Brainstem encephalitis	ANNA-1 (Hu) ANNA-2 (Ri) ANNA-3 GAD-65 mGluR1 PCA-1 (Yo) PCA-2 PCA-Tr (DNER) PNMA-1 (Ma) PNMA-2 (Ma)	ARUP Panel for ANNA-1, 2, 3, can send GAD65 through HUP, misc send out for Ma
Stiff person syndrome	Amphiphysin GAD65 Glycine receptor DPPX (PERM)	Penn Auto-Immune Encephalitis panel + Mayo MDC1 (movement disorder) panel for DPPX

To order specific antibodies: use "miscellaneous send-out" order to send individual tests to ARUP or Mayo. Make sure to include the test ID in the comments and what kind of tube they need (can look this up on the ARUP or Mayo Labs website)

Dexamethasone dosing in Neuro-Oncology for symptomatic management

Dexamethasone is used to reduce edema/ICP in symptomatic brain tumor patients.

1. Asymptomatic patient w/FLAIR hyperintense edema: no dexamethasone required

2. Symptoms + FLAIR hyperintense edema: give dexamethasone 10mg IV x1 then 4mg bid thereafter. Reevaluate symptoms after 24-48hrs. If improvement then consider reducing to 4mg daily while inpatient, and if tolerated taper slowly outpatient (e.g. 1mg decrease q7 days). Discuss taper with outpatient providers.

3. Symptoms + FLAIR hyperintense edema + moderate suspicion for CNS lymphoma: hold dexamethasone, expedite CNS lymphoma workup (MRI neuro-axis, LP for flow/cytology, ocular exam, body PET scan, Neurosurgery consult for biopsy).

4. Severe symptoms and/or large amount of FLAIR hyperintense edema/midline shift/ c/f herniation: give dexamethasone 10mg IV x1 then 4mg q6hrs bid thereafter. Reevaluate symptoms after 24-48hrs. If improvement then continue dexamethasone on slow taper (e.g. 2mg decrease q7 days). Discuss taper with outpatient providers.

5. Symptoms in setting of dexamethasone taper + FLAIR hyperintense edema: consider returning to steroid dose prior to development of new symptoms or start dexamethasone 4mg bid. Re-evaluate dose after 24-48hrs. If improvement then taper dexamethasone more slowly than schedule that precipitated symptoms.

6. Leptomeningeal disease with c/f or documented elevated ICP: Give dexamethasone 10mg IV, then 4mg q6hrs. Call neurosurgery for shunt. Re-evaluate steroid dose after 24-48hrs.

7. Leptomeningeal disease with CN/LMN symptoms: Give dexamethasone10mg IV once, then 4mg q6hrs. Call Rad onc/oncology. Re-evaluate dexamethasone dose after 24-48hrs.

8. Spinal cord compression from tumor -> give dexamethasone 10mg IV x1 then 4mg q6hrs bid thereafter. Consult radiation oncology and neurosurgery.

Re-evaluating dexamethasone dose:
- Goal is to have patients on minimum dose to reduce immunosuppression and other side effects
- If symptoms improve at 48hrs -> likely will benefit from continued steroids but will need taper.
- If no symptomatic improvement at 48hrs and amount of edema is not large -> consider discontinuing dexamethasone

Steroid Dose Equivalents

GLUCOCORTICOID COMPARISON

Drug	Equiv Dose (mg)	Rel anti-inflam potency	Rel mineralo activity	Duration (hrs)	Route
Cortisone	25.00	0.8	2	8-12	PO, IM
Hydrocortisone	20.00	1	2	8-12	PO, IM, IV
Prednisone	5	4	1	12-36	PO
Prednisolone	5	4	1	12-36	PO, IM, IV
Methylprednisolone	4	5	0	36-72	PO, IM, IV
Dexamethasone	0.75	30	0	36-72	PO, IV

NEURO-ONC

LEPTOMENINGEAL DISEASE

LMM Prognosis

Untreated, LMM prognosis is 6-8 weeks

Depending on the type of malignancy, with treatment life expectancy can range from several months to several years

LMM Symptom management

Increased ICP

- Dexamethasone dosing:
- If increased ICP suspected: scan first, prior to LP give dex 10mg IV x1 then 8mg BID while LMM workup ongoing. If c/f herniation call Neurosurgery. Re-evaluate steroid dosing at 48hrs.
- Shunt: LMM present, OP elevated and patient symptomatic-> call Neurosurgery for shunt for symptom management
- Headache: Tylenol, opioids if needed
- Nausea/Vomiting: ondansetron, metoclopromide

Cranial nerve Palsies, radiculopathy, cauda equina:

- Call radiation oncology and oncology

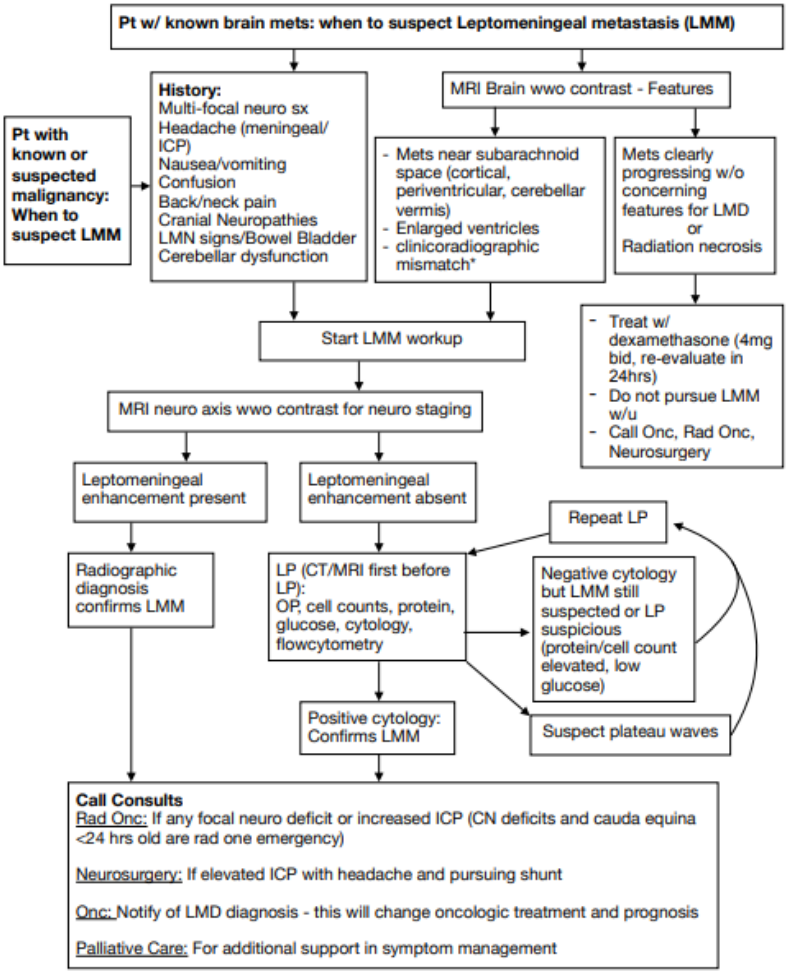
Seizures: Start ASM - generally Keppra, vimpat, onfi (pending comorbidities)

Role of Neurology: Diagnosis, determination of neurological localization of symptomatic leptomeningeal disease, initial symptomatic management of leptomeningeal disease, initiating multi-disciplinary definitive management (consulting radiation oncology, neurosurgery and oncology).

Role of Radiation Oncology: CN deficits and cauda equina <24 hrs old are radiation oncology emergency as these deficits may be reversed with immediate therapy

Role of Oncology: Oncology should be notified of LMM as prognosis and oncologic treatment plan may change. Treatment of leptomeningeal disease sometimes will involve intrathecal chemotherapy, systemic treatment with a CSF penetrant agent, or transition to hospice depending on clinical context.

Role of Palliative care: Once first steps of management are determined pall care can help with additional symptom management (ie additional pain, agitation or secretion management)



*clinicoradiographic mismatch: e.g. small mets in patient w/severe headache, severe confusion, or neurological signs not explained by mets)

NEURO-OPHTHO

NEURO-OPHTHALMOLOGIC EMERGENCIES

ACUTE THIRD NERVE PALSY

Ddx:
- Compression from PCOM aneurysm, mass, cavernous sinus thrombosis, herniation (generally involves the pupil due to the superficial position of the parasympathetic fibers on the nerve)
- Ischemia from diabetes, GCA (generally spares the pupil due to the blood flow from the vasa nervorum on the periphery on the nerve), midbrain infarction
- Inflammation from Tolossa-Hunt, Sarcoidosis, meningitis

Management:
- HCT to rule out SAH or herniation t/c CTA for aneurysm, may still need angiogram if negative.
- You may also want to get MRI for cavernous sinus syndrome.
- For pupil-sparing lesions with complete ophthalmoparesis in patients over 50 with vascular risk factors, the most likely etiology is ischemia and you may consider following clinically. Ischemic palsies almost always improve within 2-3 months. No improvement within 8 weeks warrants further evaluation. If the pupil becomes involved, then conventional angiogram is needed to exclude aneurysm.
- If pupil-sparing and partial, angiography is needed to exclude aneurysm. If there is superior division involvement (levator and superior rectus), this is often associated with compressive lesions and you need an MRI of the orbits. **If in doubt with an acute 3rd nerve, image and angiography.**

PITUITARY APOPLEXY

Symptoms:
- Classically headache w/ N/V, sudden visual loss, and ophthalmoplegia (orbital apex syndrome)
- +/- Meningismus from blood and chemical meningitis
- +/- Hypopituitarism (e.g. unstable blood pressure 2/2 adrenal crisis, hypoNa from acute SIADH)
- +/- Alteration of consciousness due to diencephalic compression and facial pain or numbness

Ddx:
- Pituitary tumor (most commonly adenoma)
- Infarction or hemorrhage (e.g. post-partum hemorrhage/Sheehan syndrome)
- If visual loss is dominant may be confused with optic neuritis
- If HA and meningeal signs are prominent may be confused with meningitis or SAH.

Exam: Check for meningeal findings, visual field loss, acuity loss, and ophthalmoparesis.

Management:
- HCT to rule out SAH when suspected LP may be required to confirm SAH or meningitis
- MRI orbits
- Immediate therapy includes steroids/hydrocortisone to prevent shock from acute hypopituitarism.
- Electrolyte abnormalities may be prominent and need to be addressed acutely.
- Labs for other pituitary deficiencies are needed but are usually less critical in the first few hours.
- Transphenoidal surgery for severe visual or ocular motility deficit (no, you won't be doing this…)

GIANT CELL ARTERITIS

Symptoms:

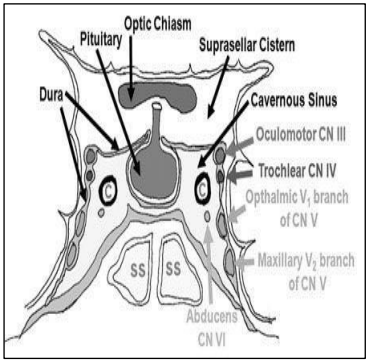
- Acute vision loss due to arteritic ischemic optic neuropathy. Can also have central retinal artery occlusion (GCA until proven otherwise), PCA stroke, oculomotor palsies (usually 3rd).
- Patient, usually female (ratio 3:1) and over 60-70 (almost unheard of <50 yrs), may have premonitory symptoms of transient monocular blindness, bright light amaurosis, transient binocular diplopia and formed visual hallucinations
- Check for symptoms like HA, scalp tenderness, jaw claudication and PMR history

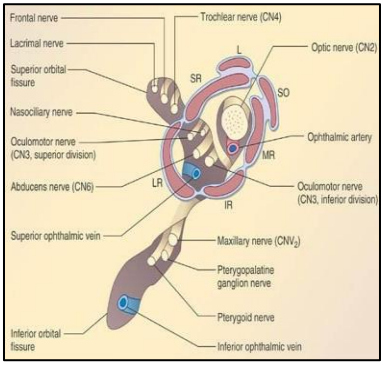
Ddx: Non-ischemic optic neuropathy or non-arteritic ischemic anterior optic neuropathy, and amaurosis fugax

Exam: Look for scalp tenderness, visual acuity loss, chalky white disc edema, and cotton wool spots.

Management:

- ESR, CRP
- Fluorescein angiography if patient in neuro-ophtho clinic
- Bx temporal artery if first artery negative and high-suspicion, then bx contralateral artery
- In the meantime, start methylprednisolone 250mg IV q6h x 3-5 days, then 1mg/kg/day PO pred (long time!)





CAVERNOUS SINUS

SOF/ORBITAL APEX

NEURO-OPHTHO

	Cavernous Sinus Syndrome	Orbital Apex Syndrome	Superior Orbital Fissure Syndrome
Symptoms	Diplopia without vision loss, proptosis less pronounced	"Blindness + SOF syndrome": Blurred vision (85%), proptosis more pronounced (70%), periorbital pain (50%)	Diplopia without vision loss, proptosis
Nerves	2 or more of: III, IV, V1, V2, VI, or oculosympathetics	**II,** III, IV, V1, VI	III, IV, V1, VI
Etiologies	Neoplasia (50%, nasopharyngeal ca #1), aneurysm, trauma, inflammation (Tolosa-Hunt)	Neoplasia (50%) > Inflammation (Tolosa-Hunt), Infection, Trauma > Vascular	Fracture, Tolosa-Hunt, Neoplasia (NHL #1)

ANISOCORIA

- Miosis: abnormally constricted pupil
- Mydriasis: abnormally dilated pupil

When evaluating anisocoria:

Step 1: Which pupil is the abnormal one? Check pupil size with both the lights on and off. If the asymmetry is worse in the dark, the smaller pupil is abnormal (because it should dilate more than it is). If it's worse in the light, the larger one is abnormal (b/c that pupil should constrict more than it is).

Step 2: Is there ptosis?

Ptosis + small pupil□ think Horner's syndrome. Anhidrosis may or may not be present depending on if it is a 3rd order neuron affected (see below).

-Test for Horner's syndrome with cocaine or apraclonidine eyedrops (see below).

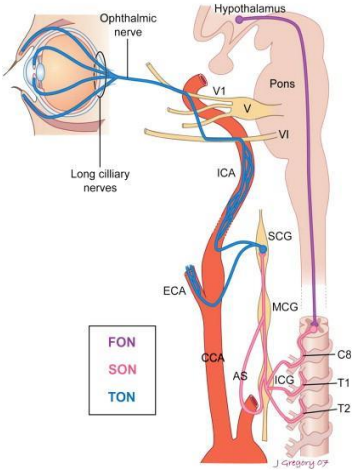
Ptosis + large pupil□ think CN3 pathology.

Ddx of anisocoria:

- CN3 lesion
- Sympathetic pathway lesion
- Meds: ipratropium nebulizer, scopolamine patch
- Physiologic anisocoria—pupillary reaction is normal but starting size of each pupil is different.
- Tonic pupil— does not constrict to light but DOES constrict to accommodation. Could be idiopathic (Adie's tonic pupil) or from a ciliary ganglion pathology□ test this with a pilocarpine eyedrop.
- Iris pathology
- Migraine, Seizure

Bilateral pupil abnormalities: b/l CN3 palsies, midbrain lesions, pontine lesions, sympathomimetics, opiates, syphilis.

Horner's syndrome:



First Order Neuron (Central)
- Lesion will lead to anhidrosis of face, arm, and trunk
- Cause: Stroke, vertebral artery dissection (causing a brainstem stroke), MS, cord compression

Second Order Neuron
- Preganglionic neuron
- Release acetylcholine
- Lesion would cause anhidrosis to JUST the face
- Cause: Pancoast tumor, brachial plexus injury

Third Order Neuron
- Postganglionic neuron
- Release norepinephrine
- No anhidrosis
- Cause: Carotid artery dissection, cavernous sinus thrombosis

Distinguishing a Horner's Location:

1. Cocaine causes no dilation on a Horner's physiologic anisocoria because it blocks the re-uptake of NE which requires it to have been released in the first place.

2. Apraclonidine is weak alpha agonist that will cause pupillary dilation in all types of Horner's syndromes due to denervation sensitivity (upregulation of receptors after not having been stimulated by NE).

3. Hydroxyamphetamine will allow for pupillary dilation if the lesion is in the first or second order neuron because it stimulates the release of NE from the presynaptic neuron. In a lesion in the third order neuron it will have no effect (in a Horner's due to a carotid dissection) because the presynaptic neuron is not functioning.

TRANSIENT MONOCULAR VISION LOSS

OVERVIEW
- Important to distinguish monocular from binocular (also know that people w/ homonymous hemianopsia do not always realize they have lost vision → typically bump into things)
  - *Localization*: monocular = anterior to optic chiasm; binocular = posterior to optic chiasm
- Most cases are due to ischemia (often either altitudinal vision loss, or complete monocular loss)

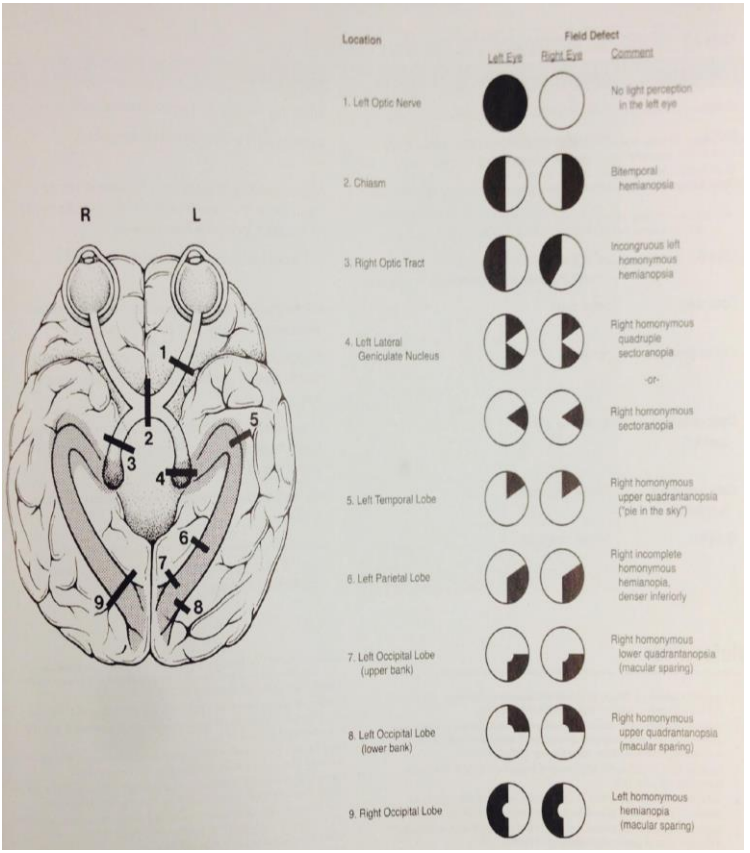
PRO TIPS
- Duration
  - Seconds → papilledema ("whiting" or "greying" out of part or all of vision)
  - Minutes → thromboembolic event, Uthoff's phenomenon
  - 20 minutes-1 hour→ migraine, post-ictal, ischemia

- Type of patient
  - Young → migraine most common
  - Old → vascular most common
  - Jaw claudication, temporal tenderness, proximal myalgias → GCA
- Field loss
  - Superior/inferior field cut (altitudinal) → vascular, retinal detachment
  - Binocular → migraine, PCA infarction, post-ictal
- Descriptors
  - Slow downward descent of vision loss → vascular, retinal detachment
  - Shifting of blurriness across visual scene → floaters, retinal detachment
  - Positive phenomena (e.g. scintillating scotomas) → ocular migraine, seizure/post-ictal, rarely can be vascular
  - Painless → vascular
  - Painful → **Optic neuritis**, angle closure glaucoma, migraine, GCA
  - Halos around lights angle closure glaucoma
  - Diplopia → GCA (ischemic nerve or muscle)
- Triggers
  - Precipitated by head turn → carotid stenosis
  - Precipitated by gaze change → trauma
  - Precipitated by heat → Uthoff's phenomenon
  - Recent cataract surgery v spontaneous hyphema (note: erythropsia)
- *FUN*doscopic findings
  - Papilledema → ischemia or inflammation
  - Disc pallor (takes 4-6 wks) → old ischemia or demyelination
  - Retinal whitening → ischemia of inner retina
  - Hollenhorst plaques → carotid/aortic disease

Vascular:
Orbital ischemia (ophthalmic artery)
Retinal ischemia (central retinal artery and its branches, central retinal vein)
Optic nerve ischemia (short posterior ciliary arteries/ophthalmic artery)
Choroidal ischemia (posterior ciliary arteries)
"Retinal migraine" (vasospastic TMVL)
Ocular diseases:
Anterior segment:
Dry eyes
Keratoconus
Hyphema
Angle closure glaucoma
Retinal detachment
Optic nerve disorders:
Papilledema (transient visual obscurations)
Optic disc drusen (transient visual obscurations)
Congenitally anomalous optic disc (transient visual obscurations)
Optic nerve compression (gaze-evoked TMVL)
Uhthoff's phenomenon (demyelination)

MANAGEMENT (to be considered given clinical picture)
- Neuro-ophthalmology and/or Ophthalmology consultation
- Labs: ESR, CRP, hypercoag panel
- Imaging: Carotid imaging, EKG, MRI, image posterior circulation if c/f VBI, EEG
- ASA/statin (vascular) vs. 1g solumedrol (GCA, MS flare) vs. AED (sz)

LOCALIZATION OF VISUAL LOSS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Location
Field Defect
Left Eye
Right Eye
Comment
1. Left Optic Nerve
No light perception in the left eye
2. Chiasm
Bitemporal hemianopsia
3. Right Optic Tract
Incongruous left homonymous hemianopsia
4. Left Lateral Geniculate Nucleus
Right homonymous quadruple sectoranopia
-or-
Right homonymous sectoranopia
5. Left Temporal Lobe
Right homonymous upper quadrantanopsia ("pie in the sky")
6. Left Parietal Lobe
Right incomplete homonymous hemianopia, denser inferiorly
7. Left Occipital Lobe (upper bank)
Right homonymous lower quadrantanopsia (macular sparing)
8. Left Occipital Lobe (lower bank)
Right homonymous upper quadrantanopsia (macular sparing)
9. Right Occipital Lobe
Left homonymous hemianopia (macular sparing)

NEURO-OPHTHO

DIPLOPIA

General rules for localization:

- Try covering one eye. If diplopia, persists, this is **monocular diplopia,** which is **basically never of neurologic origin** and almost always ophthalmologic (most often due to refractive error).
- If it resolves, it is **binocular diplopia**.
- On cover- uncover testing, an eye that is deviated out (**exotropic**) will move in when uncovered to pick up the fixation target (usually a finger or your nose). Think of an **INO or Third nerve palsy or an exotropia related to medication effect.** If the eyes move out with uncover **(esotropia), think of a sixth nerve palsy or abduction deficit**.
- Mimics of extraocular nerve palsies: myasthenia gravis, thyroid eye disease, skew deviation, decompensated phoria (common in the setting of critical illness, delirium), Wernicke's syndrome, botulism, Miller Fisher variant of Guillian-Barre Syndrome, mitochondrial d/o (CPEO: chronic progressive external ophthalmoplegia, Kearns-Sayre Syndrome), orbital wall fractures, orbital tumors, vitamin E deficiency.
- *Horizontal diplopia*: Assess for improvement with distance (if sx improve at a distance, diplopia localizes to CN III; if sx worsen w/ distance, diplopia localizes to CN VI).
- *Vertical diplopia*: Localizes to CN IV or III or skew.

1) Oculomotor nerve palsy (CN III)

1. *Innervation*: superior rectus, levator palpebrae superioris (upper branch); medial rectus, inferior rectus, inferior oblique, parasympathetic supply to pupil constrictor via ciliary ganglion
2. *Presentation*: ptosis, “down and out” eye (depressed and laterally deviated) in complete palsy. Partial third nerve palsy can present much more subtly but still will exhibit limited adduction and superior gaze. Typically diplopia will worsen with gaze convergence.
3. *Differential*: See above

2) Trochlear nerve palsy (CN IV)

1. *Innervation*: superior oblique muscle
2. *Presentation*: often subtle and not readily apparent on cursory exam. Diplopia usually described as vertical or torsional (observant patient with acquired IVth may note that one line of print is tilted; direction of downward tilt points to side of superior oblique weakness). There is a hypertropia ipsilateral to the side of superior oblique weakness; the hypertropia is more pronounced on contralateral gaze. Patients may have compensatory head tilt away from the side of the affected CN IV (e.g. left head tilt with a right fourth nerve palsy). Diplopia worst with gaze downward and away from the affected side, and with ipsilateral head tilt: patients may describe worst difficulty with reading or taking stairs.
3. *Differential*: trauma, ischemic neuropathy, tumor, demyelination, ophthalmoplegic migraine, cavernous sinus thrombosis, pituitary apoplexy, congenital

3) Abducens nerve palsy (CN VI)

1. *Innervation*: lateral rectus muscle (via contralateral abducens nucleus)
2. *Presentation*: esotropia often evident: patients may compensate by turning head towards affected side. Diplopia worsens with gaze towards the affected side as well as divergence (diplopia is worse in the distance).
3. *Differential*: ischemic palsy, trauma, increased ICP (including pseudotumor cerebri), downward transtentorial herniation, multiple sclerosis (common cause of isolated CN VI palsy from brainstem lesion in younger patients), pontine infarct, pontine glioma, cavernous sinus thrombosis (VI>III or IV),

ophthalmoplegic migraine, pituitary apoplexy, Gradenigo's syndrome (also with periorbital pain, otorrhea from mastoiditis), Wegener's granulomatosis, postviral syndrome (children), congenital (Duane's syndrome, Mōbius syndrome—both extremely rare)

FUNDUSCOPIC EXAMINATION

OPTIC NERVE HEAD PATHOLOGY

- Papilledema = optic nerve swelling due to high ICP. In the acute form it is accompanied by obscuration of retinal vessels and splinter hemorrhages. Bilateral, acuity is usually normal. DDx mass (brain or spine), hydrocephalus, venous sinus thrombosis, cerebral edema, idiopathic intracranial hypertension (pseudotumor), decreased CSF reabsorption, chronic respiratory disease.
  - *Optic disc drusen* (pseudopapilledema) is in the ddx for papilledema and reflects calcium deposition behind the nerve head confirm with orbital ultrasound
- Optic neuritis = optic nerve inflammation. Mild swelling without hemorrhage or cotton wool spots. Hallmark is pain with eye movement and loss of visual acuity.
- Non-arteritic ischemic optic neuropathy = hypoperfusion of the nerve due to compromised ciliary circulation. Associated with splinter hemorrhages, altitudinal field cut, visual loss that is worst at onset.
- Arteritic ischemic optic neuropathy = GCA. Associated with cotton wool spots (retinal ischemia) and systemic symptoms. Posterior ischemic optic neuropathy (acute visual loss with normal fundus in older patient) is also frequently temporal arteritis.

To look smart post-call mention one of the following:

- Lipid star w/ disc swelling = neuroretinitis – think infections (bartonella, syphilis, lyme, opportunistic)
- Shunt vessels (engorged connecting veins of different circulations) = compressive optic neuropathy causing restriction of venous drainage.
- Foster Kennedy syndrome = optic nerve swelling on one side (with central scotoma) and nerve pallor on the other due to mass compressing one nerve & causing increased ICP (usually meningioma). Also presents with anosmia.

NEURO-OPHTHO

NYSTAGMUS AND NYSTAGMOID MOVEMENTS

TYPE	CHARACTERISTICS	TREATMENT	ORIGIN
Periodic alternating	Horizontal- first in one direction, then stops, changes direction, usually cycles over 3 minutes.	Baclofen	Cerebellar nodulus, cervico-medullary junction
Downbeat	Fast phase downward. Usually most noticeable on down or lateral gaze.	3,4-diaminopyradine, 4-aminopyradine, clonazepam	Cervico-medullary junction, cerebellar flocculus
See-saw	One eye intorts and falls as the other extorts and rises, then alternates, kind of, like a see-saw.	Baclofen, clonazepam	Parasellar (optic chiasm), midbrain (inC, sparing riMLF)
Oculopalatal myoclonus or acquired pendular nystagmus	Pendular oscillation of the eyes and palate ("clicking noise")	GBT, Memantine, VPA, clonazepam	Central tegmental tract
Congenital Motor	Horizontal pendular and jerk nystagmus. Less with convergence. Often latent worsening.		Assoc. c many visual pathway d/o but not cause by visual loss.
Superior oblique myokymia		GBT, CBZ, propranolol	
Oculomasticatory myorhythmia	Slow convengence pendular eye movements with simultaneous jaw contractions.	Ceftriaxone	Whipple's
Congenital Sensory	Pendular		GBT, Memantine
Upbeat	Fast beat upwards		Cerebellum, medulla, midbrain
Convergence retraction	Rapid convergence and retraction movements on upgaze.		Dorsal midbrain
Rebound nystagmus	Horizontal, gaze-evoked; few beats of nystagmus in the opposite direction upon return to primary position.		Cerebellum
Brun's nystagmus	Large amplitude, low frequency with ipsilateral gaze. Small amplitude, high frequency with contralateral gaze.		Cerebellopontine angle
Spasmus nutans	Dissociated, asymmetric (occasionally monocular), high-frequency, low-amplitude pendular nystagmus. Assoc with torticollis and titubation.		Exclude chiasmal glioma and craniopharyngioma
Opsoclonus	Continuous random directional saccades	Corticosteroids, ACTH, IVIG, clonazepam	Post fossa, assoc with neuroblastoma in kids; in adults, other toxic, metabolic, parainfectious, & paraneoplastic syndromes of cerebellum and pons
Ocular flutter	Back-to-back horizontal saccades without an interval		Posterior fossa (cerebellum or PPRF), other causes similar to opsoclonus
Ocular Bobbing	Fast downward with slow upward return.		Pons (usually a hemorrhage)

NEURO-OPHTHO

PSEUDOTUMOR CEREBRI SYNDROME

(aka Idiopathic Intracranial Hypertension)

DX CRITERIA (if papilledema present)

A. Papilledema
B. Normal neurologic exam except for cranial nerve abnormalities (VIth or VIIth may be seen)
C. Neuroimaging: normal brain parenchyma (MRI with gad +/- MRV preferred)
D. Normal CSF composition
E. Elevated LP opening pressure: ≥ 25 cm H2O in adults, >28 cm H2O peds

Definite PTCS: all criteria A-E.
Probable PTCS: A-D are met, OP < 25 cmH20

DX CRITERIA (if papilledema absent)*

- Criteria B-E are met + unilateral or bilateral VIth nerve palsy

OR

- Criteria B-E are met + 3 of 4 imaging criteria are met:
  i. Empty sella
  ii. Flattening of the posterior aspect of the globe
  iii. Distention of the perioptic subarachnoid space +/- tortuous optic nerve
  iv. Transverse venous sinus stenosis

*These patients tend not to go on to develop papilledema or vision loss; headache may be difficult to treat

CLINICAL PRESENTATION

- HA is the #1 sx (non-specific characteristics, but usually daily), transient visual obscurations including unilateral or bilateral loss of vision (70%), pulsatile tinnitus (60%), diplopia if VIth nerve palsy present (50%)
- Papilledema is commonly present, but usually a chronic finding
- Loss of spontaneous venous pulsations occurs around 25 cm H2O and occurs acutely

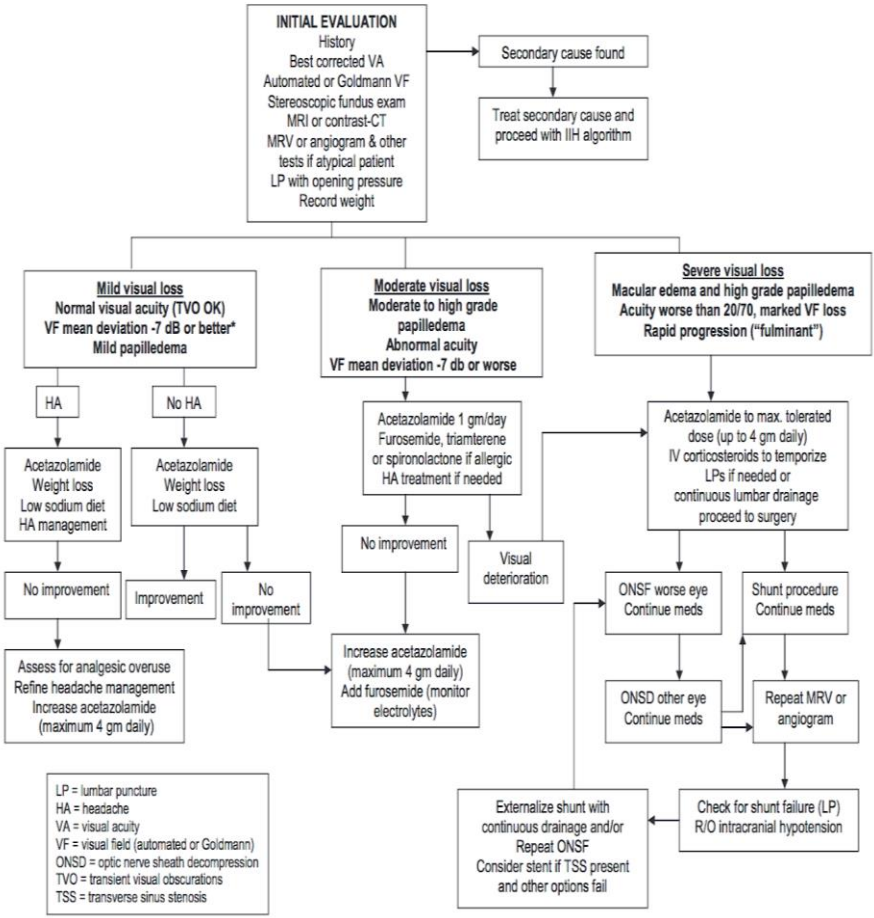
SECONDARY CAUSES OF PSEUDOTUMOR CEREBRI

Cerebral venous abnormalities	**Medications/Exposures**
Venous sinus thrombosis Bilateral jugular vein thrombosis Middle ear or mastoid infection Increased right heart pressure SVC syndrome Brachiocephalic vein thrombosis AV fistula Decreased CSF absorption (h/o meningitis or hemorrhage)	Antibiotics: tetracycline, minocycline, doxycycline, sulfa drugs Vitamin A and retinoids: hypervitaminosis, isotretinoin, ATRA Hormones: HGH, levothyroxine, levonorgestrel, anabolic steroids Anti-neoplastics: cytarabine, cyclosporine Withdrawal of chronic corticosteroids Lithium
	Medical Conditions
	Endocrine: Addison disease; hypoparathyroidism Hypercapnia: sleep apnea, obesity-hypoventilation syndrome Infectious: HIV, Lyme Other: APLAS, Sarcoidosis, SLE, OSA, PCOS, Renal failure Genetic: Turner syndrome, Down syndrome

TREATMENT

- Weight loss – cases series showed that bariatric surgery improved symptoms and papilledema
- Reduce sodium intake
- Empiric Acetazolamide 500 mg BID → Uptitrate to max 4g daily (Effects are temporary)
  - PREGNANCY: acetazolamide may be prescribed only after 20 weeks.
- Shunting (e.g. VPS) may be considered, but has a 50% failure rate.
- Optic nerve sheath fenestration for cases of rapidly progressive vision loss
- In cases of FULMINANT or RAPIDLY PROGRESSIVE VISION LOSS in pseudotumor cerebri, rule out CVST & consider high dose steroids, IV acetazolamide, optic nerve fenestration and/or placement of lumbar drain or ventriculoperitoneal shunt.

CLINICAL PATHWAY:



Suggested Reading:

Aryasit O, et al. Clinical presentation, aetiology and prognosis of orbital apex syndrome. Orbit 2013;32:91-94.

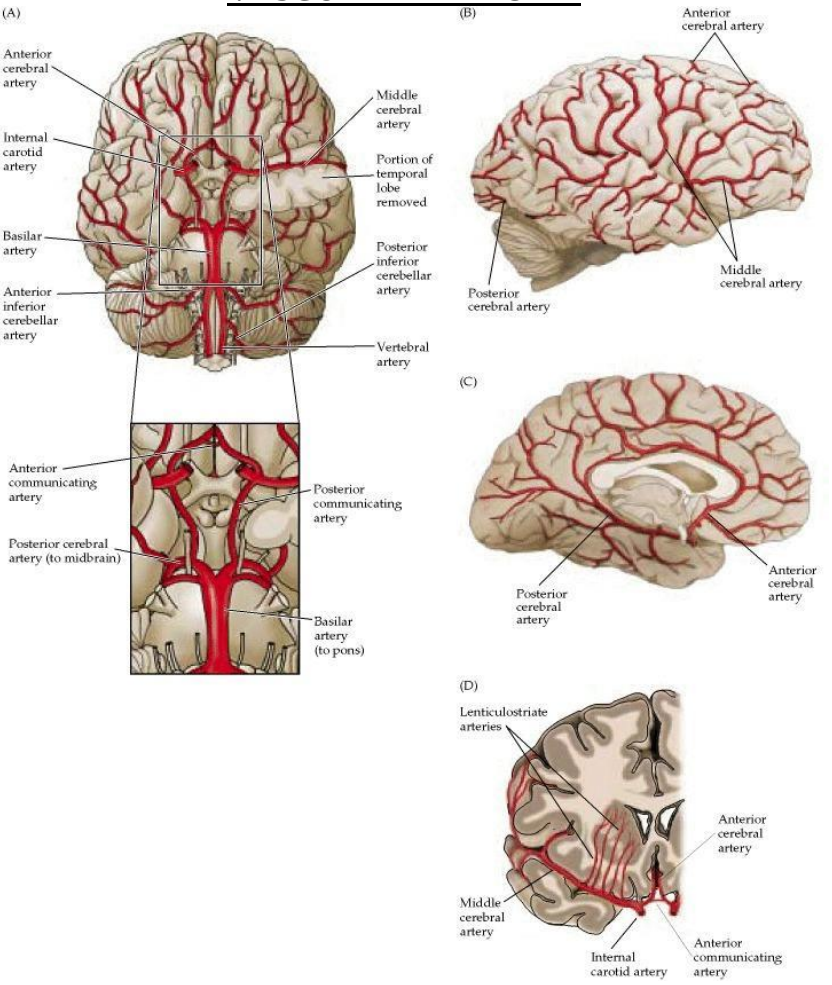
Keane JR. Cavernous sinus syndrome. JAMA Neurology 1996;53:967-971.

Liu, Volpe, and Galetta's Neuro-Ophthalmology: Diagnosis and Management. Available through the Penn Biomedical Library.

Friedman DI, et al. Diagnostic criteria for the pseudotumor cerebri syndrome in adults and children. Neurology 2013;81:1159-1165.

Friedman DI. The pseudotumor cerebri syndrome. Neurology Clinics 2014;32:363

VASCULAR ANATOMY



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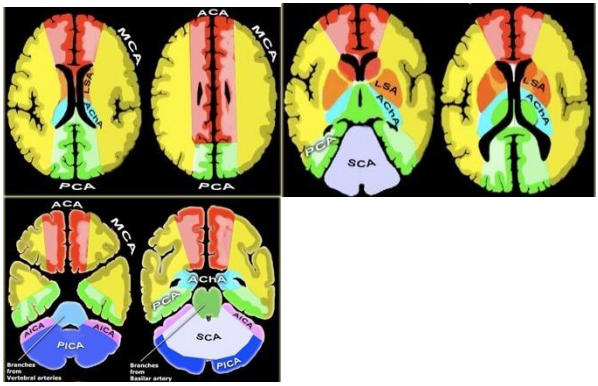

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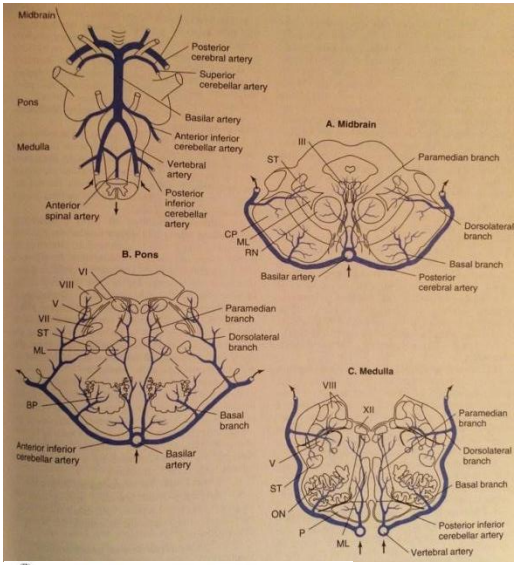
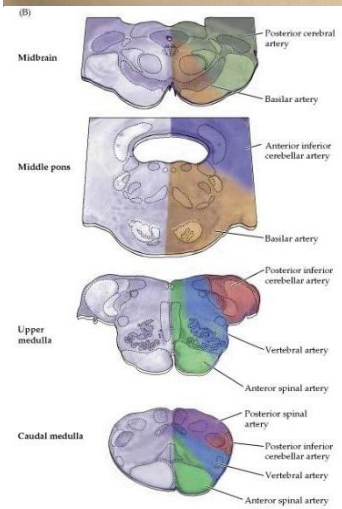




ACUTE ISCHEMIC STROKE

ED ACUTE STROKE EVALUATION

1) *Establish last confirmed normal time*
2) *NIH Stroke Scale (see Appendix D)*
3) *HCT, CTA Head and Neck /CTP as soon as possible*
4) Vitals, FSG, CBC, panel, coags, type & screen
5) If possible tenecteplase (TNK) or tPA candidate, notify pharmacy
6) If stroke is acute/<24hrs, call stroke fellow if not already

Stroke Mimics

Intoxication
Mass
Hyper/Hypoglycemia
Recrudescence
Demyelination
Conversion disorder

called

FLOOR EVALUATION & MANAGEMENT
-Admit using "stroke/TIA admission order set"
- Note template is ".strokenote"
I. Stroke precautions
[] HOB flat for 24 hrs only if perfusional/tolerated by patient. RCT without clinical benefit
[] IV fluids: NS @ 100 cc/hr (unless CHF, ESRD)
[] permissive HTN: goal SBP<220, MAP<140, hold home BP meds (except ½ dose β-blocker)
[] normothermia: tylenol PRN for temp > 100.4
[] normoglycemia: FSG/ISS
[] neurochecks q4hrs
[] bedside dysphagia screen
II. Diagnostics
[] MRI brain stroke protocol (w/o contrast)
[] Vascular imaging:
Anterior Circulation: CUS/TCD vs. MRA vs. CTA
Posterior Circulation: MRA vs. CTA
[] TTE (with bubble for PFO, with contrast for LV thrombus).
Consider TEE if unclear etiology and embolic appearance
[] EKG
[] telemetry
[] CXR
[] Labs: lipid panel, LFTs, troponin, ESR, RPR, A1C, TSH if new-onset a-fib
[] UA, UDS
[] blood cultures if concern for endocarditis
III. Treatment
[] Aspirin 325 mg PO or 300 mg PR
[] Atorvastatin 80 mg daily
[] Heparin SQ 5000 units q12hrs/Lovenox 40mg daily

ETIOLOGIES

Cardioembolic (20%)
- Afib, pAF
- Systolic HF (EF <30%) with apical wall hypokinesis
- Valvular disease, endocarditis, ?PFO

Large Vessel Disease (25%)
- > 50% stenosis of large extracranial (aorta, common carotid, ICA) or intracranial (ICA, basilar) vessel
- ICA dz: need CEA vs. stent in < 2 weeks

Small Vessel Disease (15%)
- DM, HTN, dyslipidemia, tobacco use

Cryptogenic (25%)
- Etiology unknown or several are possible (e.g. Afib + carotid stenosis)

Other (15%)
- Dissection
- Autoimmune disease (SLE, APLAS, PACNS)
- Systemic inflammatory diseases (Sarcoidosis)
- Aortic arch atheroma
- Malignancy/Chemo (e.g. anthracycline-induced cardiomyopathy)
- Drugs (cocaine vasculitis, amphetamines)

CHOOSING AN ANTITHROMBOTIC
- ASA 325mg for all comers (hold x24 hrs post TNK/tPA)

ASA 325mg +Plavix 600mg load, then 75mg daily for 21 days w/ ASA 81 mg as DAPT, followed by ASA 81mg daily monotherapy for minor strokes (NIHSS<3) or high risk TIAs (ABCD2 >4)- POINT TRIAL

ASA 325mg + Plavix 300mg load then 75mg daily for 3 months w/ ASA as DAPT, followed by ASA 81mg monotherapy, for severe intracranial athero—SAMMPRIS trial

-If large stroke/bleeding risk, d/w fellow. Can do ASA 325mg daily vs Plavix 300-600mg load, then 75mg daily

- Resume AC for pts on AC after 7-10d (14d if large infarct)
- Empiric AC *contraindicated* for routine secondary stroke ppx, higher bleeding risk (WARSS trial)

STROKE SYNDROMES

EPONYM/ARTERY	ANATOMY	SYMPTOMS
ACA	Medial frontal & parietal	Contra leg>arm weak Abulia
Recurrent Artery of Huebner (branch of A1 segment)	Anterioinferior Caudate Putamen Anterior Limb of IC	Contra face & arm weakness (Huebner) Contra leg weakness (A1 segment)
MCA- Superior M2 (anterior)		F & A > L weakness/numbness Expressive aphasia (dom, Broca's) Hemineglect (non-dom)
MC- Inferior M2 (posterior)		Homo hemi/upper quadrantanopsia Receptive aphasia (dom, Wernicke's) Constructional apraxia (non-dom)
Gerstmann syndrome (partial MCA)	Dom inferior parietal lobe (angular gyrus)	Agraphia/alexia Finger agnosia Acalculia R-L confusion
Unilateral PCA	Occipital and infero-medial temporal lobes, posterior thalamus	Homo hemianopsia with mac sparing +/- Alexia without agraphia, anomias
Balint syndrome (bilat PCA)	Bilateral parietooccipital	Optic ataxia Ocular apraxia Asimultagnosia
Anton syndrome (bilat PCA or top of the basilar)	Bilateral occipital lobes	Cortical blindness with denial +/- Hallucinations ("release")
PCA Callosal branch	Dom occipital lobe + splenium of CC	Alexia without agraphia, or "pure word blindness"
Dejerine-Roussy or "thalamic pain syndrome" (PCA branch)	Thalamus	Contra hemisensory loss Contra hemibody pain
Weber (PCA penetrators)	Midbrain, anterior	Ipsi CN III palsy, contra weakness
Claude (PCA penetrators)	Midbrain, tegmentum	Ipsi CN IIIrd, contra tremor/ataxia, +/- Contra weak and numb
Benedikt (PCA penetrators)	Midbrain, tegmentum	Ipsi CN IIIrd, contral ataxia and chorea, hemisensory loss
Raymond (basilar paramedian branches)	Pons, ventral-medial	Ipsi CN VI palsy (*spares CNVII*) Contra weakness
Millard-Gubler (basilar shorts and paramedian branches)	Pons, basis pontis and VI and VII fascicles	Ipsi CN VI and VII palsies Contra weakness
Foville (basilar shorts and paramedian branches)	Pons, tegmentum and caudal third	Ipsi VI/PPRF (gaze) & VII palsies Contra weakness, sensory loss
Marie-Foix (basilar/AICA)	Pons, lateral	Ipsi ataxia, contra weak and numb
Locked-in syndrome (basilar)	Bilateral ventral pons	Bilat F/A/L weakness Bilat VI palsies, Aphonia
Wallenberg or lateral medullary syndrome (vert>PICA)	Medulla, lateral	Ipsi face sensory loss (CN V) Ipsi ataxia, Nystagmus, N/V, Vertigo Hoarseness, Dysphagia Ipsi Horner's, Contra body sense los
Anterior Spinal Artery or "Dejerine syndrome"	Medulla, medial	Ipsi tongue deviation)Contra weak Contra vib/proprio loss (ML)

DIFFERENTIAL DIAGNOSIS FOR RESTRICTED DIFFUSION

*Subacute/chronic. B = basal ganglia; CJD = Creutzfeldt-Jakob disease; CO = carbon monoxide; HSE = herpes simplex encephalitis; H-I = hypoxic-ischemic; PRES = posterior reversible encephalopathy syndrome; RCVS = reversible cerebral vasoconstrictive syndrome; T = thalamus.

IV TNK (Tenecteplase) and rt-PA (Alteplase)

EXCLUSION CRITERIA

CT evidence of hemorrhage
Time last seen normal > 4.5 hours or unknown
Allergy to tPA
Suspicion of Subarachnoid Hemorrhage
Intracranial dissection (not carotid/vert)
SBP > 185 or DBP > 110 resistant to treatment
Platelet count <100,000/Known bleeding disorder
Neurosurgery or serious head trauma < 3 mos
INR > 1.7 if patient on warfarin, UFH with elevated PTT >40, LMWH (therapeutic dose) in 24 hrs /DOAC in 48 hrs
Glucose <50 or >400
Active or systemic bleeding prior 3 weeks

RELATIVE EXCLUSION CRITERIA

CT evidence of early severe hypo density/mass effect If presents within 3-4.5 hours
NIHSS >25, history DM+ stroke, >1/3 MCA infarcted
Puncture at Non-compressible site with 1 week
Recent lumbar puncture
Recent stroke < 3 months ago
Rapid improvement of neurologic deficit
AVM or aneurysm (generally okay if <10mm)
Major surgery or systemic trauma < 2 wks ago
Known CNS Neoplasm
Pregnancy (uterine bleeding consult OGBYN)
Prior Intracerebral Hemorrhage-If etiology reversed ie clipped aneurysm/traumatic

IV TNK Dosing: FIRST LINE

Total dose: **0.25 mg/kg** (maximum dose: 25 mg) (this will be calculated by the pharmacy team)
- administer as a single IV bolus over 5-10 seconds
- Incompatible with dextrose solutions: dextrose-containing lines must be flushed with a saline solution before and after administration

IV rt-PA Dosing

Total dose: **0.9 mg/kg** (maximum dose: 90 mg) (this will be calculated by the pharmacy team)
- 10% of the total dose administered as an IV bolus over 1 minute
- remaining 90% infused over 60 minutes

** A dedicated IV line is required for tPA

	Alteplase (t-PA)	Tenecteplase (TNK)
Indication	• AIS FDA-approved agent • Can also be used for massive PE at different dose • Approved for use in STEMI as alternative agent	• AIS off-label • Possibly preferred if eligible to undergo mechanical thrombectomy • Only labeled use is STEMI at different dose – agent of choice
Dosing (AIS)	• **0.9 mg/kg, max dose 90 mg over 60 minutes** • **Initial 10% of dose given as bolus over 1 minute**	• **0.25 mg/kg, max dose 25 mg** • **Given over 5-10 seconds**
Timing for AIS	• Within 3 hours of symptom onset (labeled use) • Within 3-4.5 hours (off-label)	• Within 4.5 hours of symptom onset
Preparation	• Reconstitution and removal of bolus dose • Removal of drug not to be given from remaining quantity • Infusion must then be assembled	• Reconstituted with supplied syringe and SWFI

Misc. Logistics:
- To expedite door-to-needle times, can consider pulling the patient out of the CT scanner for thrombolytic therapy prior to continuing with CTA/CTP.
- For **PPMC:** Of note, at PPMC there is an ED pharmacist from 11-8pm during the week to mix tPA/TNK at bedside.
- For **PPMC** and **PAH:** Early transfer guidelines: cortical signs, plus hemiplegia. If you see these, have the ED call the transfer center ASAP for transfer to HUP.

RISKS/PRECAUTIONS

- Internal or external bleeding
- Thromboembolism (increased risk in patients with high probability of left heart thrombus)
- Arrhythmias (coronary thrombolysis may result in reperfusion arrhythmias)
- Hypersensitivity reactions
- Cholesterol embolism (rare)

POST-THROMBOLYTIC MANAGEMENT

- as above for routine stroke admission EXCEPT

[] INCU or NICU bed

[] BP and neurochecks: q15 min x 2 hrs, then q30 min x 6 hrs, then q1 hr x 16 hrs

[] keep SBP<180, DBP<105 □ then liberalize to SBP <220, MAP <140 if no endovascular tx done

[] no aspirin or heparin for 24 hrs

[] repeat HCT 24 hours post TNK/tPA (if negative for bleeding: start aspirin, SQH)

[] STAT HCT for any change in neuro exam

[] bleeding precautions: minimize invasive procedures; compress puncture sites and assess for hematoma

BLOOD PRESSURE MANAGEMENT

MEDICATIONS	BOLUS	INFUSION
Labetalol	10 or 20 mg may repeat every 10 min, maximum total 150 mg	2 – 8 mg/min
Nicardipine	n/a	Begin at 5 mg/hr Increase rate by 2.5 every 10 min Maximum rate 15 mg/hr

IV TNK or rt-PA REVERSAL PROTOCOL

- STAT head CT (if concern for ICH)
- STAT labs: PT/PTT, platelets, fibrinogen, type & cross
- Enter "Reversal of thrombolytic agent" order and Call blood bank HUP PAV (267-862-1649), PPMC (215-662-8836), or PAH (215-829-3218)
  - 2 units thawed plasma (immediately available, unmatched if necessary)
  - 2 doses platelets (4 units)
  - 2 bags (5 units/bag) with total of 10 units of cryo (will need to thaw, start as soon as available → check fibrinogen 1 hour after infusion, re-transfuse goal fibrinogen>150)
- If blood products are contraindicated or declined by patient/family, tranexamic acid can be considered

** Notify stroke attending/fellow immediately.

** Transfusion attending HUP: 215-838-8449

ANGIOEDEMA

- 1-2% of patients treated
- 0.3mg IV and or inhaled epinephrine (repeat q5min x3 max), 125mg IV solumedrol, 25mg IV Benadryl
- Monitor airway, may need intubation

NEUROVASCULAR

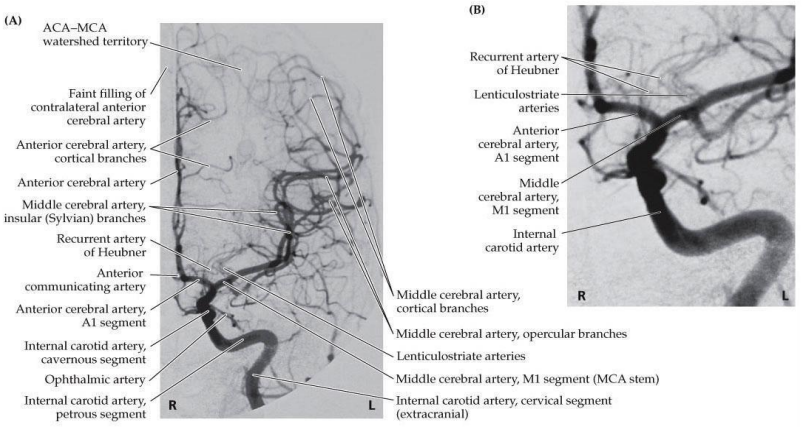
ENDOVASCULAR RESCUE STEPS FOR LARGE VESSEL OCCLUSION

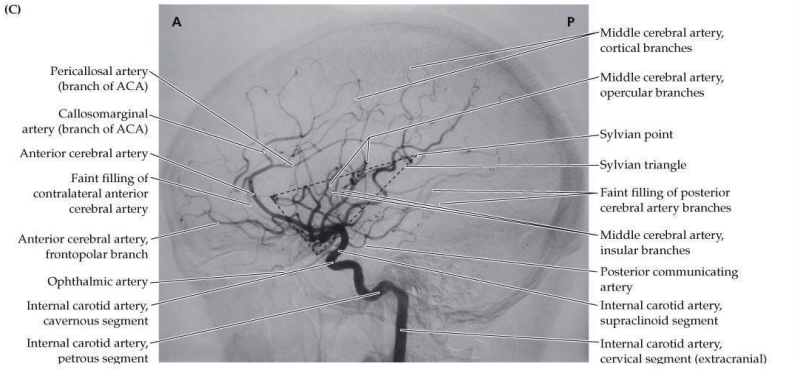
1) Consult JAR is responsible for ordering non-con HCT, CTA H/N, CTP, and neuro IR consult (prior to patient arrival if an OSH transfer)
2) There will be an EPIC secure chat about the patient details
3) Meet patient from PennStar/ED/in-hospital stroke at (1) helipad for patients being flown or in the ED for (2) ground transport (patient should be brought directly to scanner if needing repeat scan, vs to OR depending on discussion with fellow), to be joined by NICU Clinical Lead RN (215-380-4592). *NOTE: in past stroke fellow would come in. That will not be routine anymore. If decision is to do thrombectomy on call Neuro IR fellow will assume care of patient (in CT scanner or over in Neuro IR) and you are free to do other consults)*
4) Must have 18-gauge IV must be in **right arm** for CTP (20 for CTA H/N)
5) CT head for ASPECTS and rule out ICH, CTA head/neck to determine clot location
6) Fellow and Attending will discuss with NeuroIR
7) Disposition: NICU if unstable or critically ill or thrombectomy, INCU, if hemodynamically stable, no thrombectomy

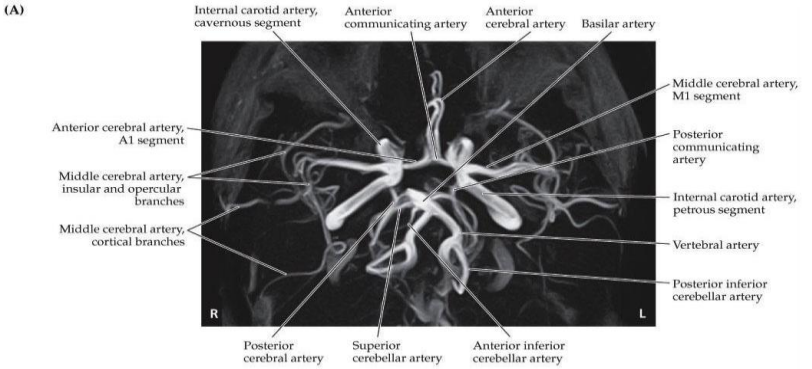
RECOMMENDATIONS FOR ENDOVASCULAR RESCUE*

- Acute occlusion of proximal anterior circulation within 24 hours favorable CTP/ASPECTS score (>6)
- Acute occlusion of basilar, vertebral artery, b/l vertebral arteries possible >24 hours of LKN
- Studies to know: MR CLEAN, EXTEND-IA, DAWN, DEFUSE 3

NEUROVASCULAR







TIA

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Transient ischemic attack is a *clinical diagnosis* of focal neurologic deficits that correlate with a compromised vascular territory lasting for <24 hours. **If neuroimaging confirms infarction regardless of symptom duration, it is no longer a TIA.**

ABCD^2 SCORE

Risk of stroke within 2 days of a TIA

Age ≥60 years [1 point]
Blood pressure ≥140/90 mm Hg [1 point]
Clinical features: unilateral weakness [2 points], speech impairment without weakness [1 point]
Duration ≥60 min [2 points] or 10–59 min [1 point]
Diabetes [1 point]

Score 6–7 = High risk = 8.1% 2-day risk
4–5 = Moderate risk = 4.1%
0–3 = Low risk = 1.0%

Typically, patients should be admitted for an ABCD2 score of >3. But obviously you should discuss this with your fellow and consider the remainder of the clinical history. A 59 year old man with two prior heart attacks and acute, transient left hemiplegia for 5 minutes (ABCD2 score 2) should probably be admitted…

IF SUSPICIOUS FOR TIA

ED at HUP and PPMC has a "TIA Pathway" that they should use for suspected TIA cases (i.e. complete resolution of symptoms).

- Treat like a stroke (head of bed flat, IVF, permissive HTN, ASA, DAPT if ABCD >4 per POINT Trial)
- Stroke work-up including stroke labs (HgA1c, lipid panel, NT-proBNP, RPR, D-dimer, ESR, and UDS) and vessel imaging with CTA/MRA head and neck and TTE
- Confirm absence of infarction with MRI if possible
- Infarctions may be "MRI negative" (no restricted diffusion) in 10-20% of cases of posterior circulation disease, but is quite rare for anterior circulation strokes

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SECONDARY STROKE PREVENTION

***** Identifying stroke etiology is key to effective secondary stroke prevention *****

CARDIOEMBOLIC STROKES

1. **Atrial Fibrillation (AF or PAF)**: Telemetry during hospitalization (AF found in ~5%). In cryptogenic stroke, consider 28-day Mobile Cardiac Outpatient Telemetry (MCOT), (AF found in another 10-15%)—place order in EPIC and route to Kim Sears. Patients may be considered for placement of subcutaneous LINQ device for long-term monitoring. Contact Dr. Matthew Hutchinson's office (HUP cardiology) or through Ellen McPartland (PAH 267-266-06 97) to set up appointment for placement. Treatment should include life-long anticoagulation unless contraindicated. Start date for anticoagulation should be considered in the context of subsequent stroke risk and risk of hemorrhagic conversion (typically 1-2 weeks):

ANTICOAG	MECHANISM	DOSE	MONITOR	REVERSE	TRIALS
Warfarin (Coumadin)	Inhibits vitamin K dependent factors $t_{1/2}$=20-60hrs	2-10mg QD	INR goal 2-3	Vit K + FFP in systemic bleed Vit K + aPCC for intracranial hemorrhage	*ACTIVE W* (2006) warfarin more effective than ASA plus Plavix and similar bleed risk
Dabigatran (Pradaxa)	Direct Thrombin (IIa) inhibitor $t_{1/2}$=12-17hrs	150mg BID (adjust to 110mg BID for CrCl)	None PTT may elevate	Idracizumab (5g IV x1)	*RE-LY* (2009) dabigatran superior to warfarin for stroke/VTE but more GI bleeding & MI
Rivaroxaban (Xarelto)	Direct Factor Xa inhibitor $t_{1/2}$=5-9hrs	20mg qd	None	Andexanet alfa 400mg or 800mg, vit K + aPCC can be considered	*ROCKET-AF* (2011) rivaroxaban non-inferior to warfarin for stroke, superior for major bleeding & ICH, but inferior for GI bleeding
Apixaban (Eliquis)	Direct and competitive Factor Xa inhibitor $t_{1/2}$=8-15hrs	5mg BID (2.5mg BID if 2 of 3 are met: age>80, wt <60kg, or low CrCl)	None	Andexanet alfa 400mg or 800mg IV, vit K + aPCC can be considered	*ARISTOTLE* (2011) apixaban superior to warfarin for stroke, ICH, major bleeding & death; similar GI bleeding risk *AVERROES* (2011) apixaban superior to ASA and similar bleed risk among "bad coumadin candidates"
Edoxaban (Savaysa)	Direct Factor Xa inhibitor $t_{1/2}$=10-14hrs	60mg qd	None	No reversal agent, vit K + aPCC can be considered	*ENGAGE-AF* (2013) edoxaban non-inferior to warfarin for preventing stroke & VTE with lower bleeding risk

Selecting a DOAC for stroke prevention	
Stroke + non-valvular Afib +	
Normal renal function	Apixaban > dabigatran > rivaroxaban, edoxaban, warfarin
DVT or PE	Apixaban, rivaroxaban, dabigatran (all non-inferior to warfarin) > edoxaban, warfarin, LMWH
CAD or **Peripheral Artery Disease**	No comparison, warfarin best studied, NOAC preferable
Acute coronary syndrome	No comparison, lowest dose NOAC preferable when dual AP necessary
High risk of GI bleeding	Apixaban > warfarin > dabigatran, edoxaban, rivaroxaban
Stage III CKD	Apixaban > rivaroxaban, edoxaban > dabigatran, warfarin
On hemodialysis	Warfarin (NOACs contraindicated)

CHA_2DS_2-Vasc score predicts risk of recurrent thromboembolic event (TE):

RISK FACTOR	POINTS
Female (*sorry ladies*)	1
Congestive heart failure	1
Hypertension	1
Age	65-74: 1 ≥75: 2
Diabetes mellitus	1
Stroke/TIA/thromboembolism	2
Vascular disease	1

CHA_2DS_2-Vasc SCORE	Annual TE rate
0	0%
1	0.6%
2	1.6%
3	3.9%
4	1.9%
5	3.2%
6	3.6%
7	8%
8	11.1%
9	100%

Objective is to treat patients with **CHA_2DS_2-Vasc** score of 2 or more points with therapeutic anticoagulation (this is for someone who has afib but hasn't not had a stroke yet).

2. **Low EF (<35%)**: Every acute stroke patient should have an echocardiogram performed during admission. AC may be considered with respect to secondary stroke prevention in patients with systolic HF *and* apical or anterior wall motion abnormalities.

3. **Cardiac Thrombus:** Typically seen after MI or in setting of identified wall hypokinesis or regional wall motion abnormality (e.g. atrial septal aneurysm). This is a very high-risk lesion with respect to early stroke recurrence. Anticoagulation for at least 3 months is appropriate, repeat echo prior to stopping AC.

4. **Valvular Disease:** For native rheumatic MV disease, warfarin should be considered. For native non-rheumatic AV and MV disease, antiplatelet agent may be sufficient depending on the case specifics. For MV calcifications, antiplatelet agent should be sufficient. For MV prolapse, long term AC with warfarin should be considered.

5. **Aortic Arch Disease**: If lesion >4mm, aspirin is recommended, and dual antiplatelet therapy w/ clopidogrel can be considered and is superior to anticoagulation. Also need to place patient on statin.

6. **PFO:** Stroke is theoretically plausible via two mechanisms: (1) paradoxical embolism from DVT bypassing the pulmonary circulation, or (2) thrombus formation at irritated cardiac focus where PFO lies. Based on the results of several trials, surgical closure is not superior to medical therapy (CLOSURE I, RESPECT, PC trial—all in NEJM 2012-2013). Still you may find that cardiologists are eager to close PFOs, and one meta-analysis suggests a small reduction in recurrent thromboembolic events with closure. Most patients under 60 should get a bubble study as part of their TTE.

LARGE VESSEL DISEASE

1. **Extra-cranial Carotid Disease**: If symptomatic stenosis >70%, recommend CEA if perioperative risk <6%. If symptomatic stenosis is 50-70%, would strongly consider CEA within 2 weeks depending on age, sex, cardiac risk. Long-term outcomes appear to be the same regardless of stenting vs. CEA. Stenting could be considered in younger asymptomatic patients. Stenting should also be considered in high risk surgical patients (COPD, prior neck surgery or radiation) or patients with active cardiac disease (in which case they may need carotid stent prior to or at the same time as cardiac procedure). If CEA is indicated, should have it done within 2 weeks of the vascular event (burden of repeat vascular events very high upfront). External-to-internal carotid bypass is no longer supported. Long-term modifiable risk factors should be addressed as outlined below, in addition to antiplatelet therapy. Any patient **>70% asymptomatic stenosis** email brett.cucchiara@pennmedicine.upenn.edu for **CREST-2 enrollment.**

2. **Extra-cranial Vertebrobasilar Disease:** Optimize long-term modifiable risk factors as outlined below. If recently active while on antiplatelet monotherapy, can often consider 3 months of dual antiplatelet therapy. If lesion continues to be symptomatic, should consider endovascular intervention.

3. **Intra-cranial atherosclerosis:** Aggressively optimize long-term modifiable risk factors as outlined below including antiplatelet therapy. If symptomatic, strongly consider a 3 month course of dual antiplatelet therapy with aspirin and plavix. Endovascular intervention is not superior to medical management (SAMMPRIS, 2011). There is also no benefit of warfarin over ASA (WASID, 2005).

4. **Dissection**: Very controversial topic. The risk is low for recurrent stroke based on the CADISS trial. Most patients are treated with aspirin (or DAPT if TIA with high ABCD score) but you could consider 3 months of AC and then repeat vascular imaging to evaluate the lesion. If dissection is not healed at that point, you can consider continuing anticoagulation. Very rarely you could consider stenting an acutely perfusional lesion, but this is quite difficult and not commonly performed.

SMALL VESSEL DISEASE

Classically this has been considered to be lacunar disease, or infarction of the small deep penetrating arteries affecting the basal ganglia, thalamus, pons, and deep white matter structures such as the internal capsule. However, because up to 20% of lacunar strokes are embolic (cardiac, aortic, carotid), do not simply assume small vessel in etiology based on radiographic appearance. In patients with small vessel atherosclerosis, secondary prevention is based on reducing long-term modifiable risk factors as outlined below, in addition to antiplatelet therapy.

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CRYPTOGENIC STROKE

Often due to incomplete diagnostic battery, but occult etiologies should be further investigated. Once determined (e.g. paroxysmal atrial fibrillation, occult malignancy, etc), the specific etiology ought to be targeted with treatment and secondary stroke prevention with an antiplatelet agent, statin, blood pressure and glucose control should be continued. The NAVIGATE-ESUS randomized cryptogenic stroke patients to therapeutic anticoagulation (Xarelto) versus antiplatelet therapy and found no difference in outcome. The ARCADIA TRIAL is ongoing and randomizes patients with cryptogenic stroke and left atrial cardiopathy to Apixaban vs ASA. Ask stroke attending to determine if your patient is eligible for participation.

*****Antiplatelet therapy in secondary stroke prevention*****

There are several available anti-platelet agents that are effective with respect to secondary stroke prevention. Typically, if patient is on no antiplatelet prior to stroke, you can start ASA. If patient has stroke while on ASA, and there is no clear intervenable cause for stroke, you can consider transition to an alternative antiplatelet agent such as Plavix. Dual antiplatelet therapy with ASA and plavix is considered in patients with high risk TIA or minor stroke (POINT/CHANCE) or large artery atherosclerosis (SAMMPRIS). Patients on therapeutic anticoagulation do not routinely require antiplatelet therapy for the purposes of secondary stroke prevention, but many patients on therapeutic AC may be still require antiplatelet therapy for cardiovascular purposes. When starting AC in cardiac patients, it is often appropriate to contact the patient's cardiologist to address this issue.

Antiplatelet agents in setting of a primary ICH should generally be avoided in routine practice. In primary ICH, antiplatelet agents are typically avoided indefinitely, but if the source of ICH is clearly identified and controlled (securing aneurysm, controlling HTN, etc.) then this can be readdressed depending on the patient's overall vascular risk.

*****Long-term modifiable risk factors*****

1. Hypertension: goal BP <140/80 (SBP <130 if recent lacunar infarction is reasonable), no clear superior medication regimen
2. Diabetes: goal HgBA1c < 7
3. Hyperlipidemia: highest tolerable dose of statin (atorvastatin 80mg vs. Crestor 40mg)
4. Smoking: counseling and nicotine replacement therapy or oral smoking cessation medications
5. Alcohol intake: ≤ 2 drinks per day for men, and ≤ 1 drink per day for women
6. Exercise: > 30 mins per day of moderate-intensity physical exercise at least 3 times per week
7. Mediterranean diet. Encourage extra-virgin olive oil, nuts, fresh fruit, fish. Limit salt intake to <2.4g/d.

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INTRACRANIAL HEMORRHAGE

DIFFERENTIAL DIAGNOSIS

(1) Hypertension

(2) Amyloid angiopathy

(3) Coagulopathy (including anticoagulation

(4) AVM/aneurysm

(5) Trauma

(6) **Venous sinus thrombosis (Always consider!)**

(7) Neoplasm

(8) Hemorrhagic transformation of ischemic stroke

(9) Septic emboli

(10) Vasculitis

(11) Cocaine/amphetamines

(12) HSV encephalitis

INITIAL MANAGEMENT & EVALUATION

I. Precautions
- generally NICU or INCU bed
- HOB > 30°
- goal SBP <160
- dysphagia screen

II. Diagnostics
- Labs: coags (goal INR < 1.5), platelets (goal >100), ESR
- repeat head CT in 12-24 hrs (stat if signs of deterioration)
- t/c MRI brain with GAD
- CTA vs MRA
- UDS
- EKG, telemetry
- if evidence of endocarditis: blood cultures, TTE and possible TEE

Blood most likely to have underlying tumor
Lung
Breast
Colon
Tumors most likely to bleed in the brain
Melanoma
Choriocarcinoma
Renal cell carcinoma
Papillary thyroid carcinoma
Glioblastoma multiforme
Hepatocellular carcinoma

III. Treatment
- reverse anticoagulation if INR > 1.5
  - aPCC (activated prothrombin complex concentrate) contains factors II, VII, IX, X, C, S
  - If unavailable, give FFP 2-4 units
  - Vitamin K 10 mg IV (for delayed effect)
  - Idracizumab 5mg IV for patients on dabigatran
  - Andexanet alfa for apixaban or rivaroxaban:
  - - low dose = 400mg for apix </= 5mg or rivaroxaban </= 10 mg last dose < 8 hrs or at any dose > 8hrs
  - - high dose = 800mg for apix > 5mg or rovarox > 10 hrs last dose within 8 hrs
- transfuse platelets to >100K
- hold ASA and anticoagulation
- hold statin
- hold SQH until bleed stable for at least 24 hours

NEUROSURGERY CONSULT
- large bleed
- mass effect/midline shift
- intraventricular involvement (may need EVD)

- cerebellar hemorrhage (consult early)

ICH SCORE				
Glasgow Coma Score	**ICH Volume***	**Location**	**Intraventricular hemorrhage**	**Age**
3-4 [2 points]	≥ 30 cm^3 [1 point]	Infratentorial [1 point]	Yes [1 point]	≥ 80 [1 point]
5-12 [1 point]	< 30 cm^3 [0 poins]	Supratentorial [0 points]	No [0 points]	< 80 [0 points]
13-15 [0 points]				

*ICH volume: [(max length) x (max width) x (# of slices) x (slice thickness)] / 2
30-day mortality (Hemphill original derivation trial): 0 – 0%; 1 – 13%, 2 – 26%, 3 – 72%, 4 – 97%, 5 – 100%

SUBARACHNOID HEMORRHAGE

INITIAL CHARACTERIZATION

I. Etiology

- Aneurysmal SAH
  - 80-85% of all non-traumatic SAH
  - Risk of vasospasm, Highest risk of poor outcomes
- Angiogram-negative SAH
  - Still likely to be aneurysmal (10-20% of angio-neg SAH), or else the aneurysm obliterated or vasospasm is hiding the aneurysm
  - Recommend repeat CTA in 1 week
- Perimesencephalic SAH
  - 10% of all SAH and 2/3 of non-aneurysmal SAH
  - HA milder and more progressive than aneurysm rupture
  - Occurs from ruptured anterior veins in prepontine or interpeduncular cistern, no IVH or IPH
  - Risk of re-bleed or delayed ischemia is negligible, outcome is excellent
- Traumatic SAH (usually superficial cortical or basal forebrain bleeds)
- Dissection (Intradural Vertebral > Carotid)
- Coagulopathic SAH (iatrogenic, secondary to systemic illness)
- Dural AVF (may be associated with prior head injury or venous thrombosis→ creating dural shunt)
- Spinal AVM or AVF (more common in pts <20 y/o)
  - Rebleed risk is high (~50%) in spinal & dural AVMs
- ICH w/ SAH extension
- Other: Mycotic aneurysm, cocaine abuse, Moya Moya, pituitary apoplexy (w/ preceding loss of visual acuity)

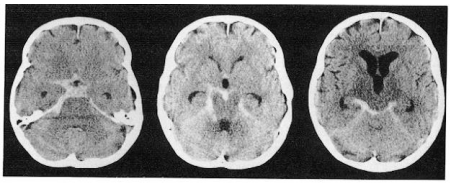

FIG 1. *Computed tomographic scan of patient with perimesencephalic hemorrhage. All perimesencephalic cisterns are completely filled with blood, but extravasated blood does not extend beyond chiasmatic cistern, central part of sylvian fissures, and posterior part of frontal interhemispheric fissure. There is no blood in lateral part of sylvian fissures or anterior part of interhemispheric fissure, and there is no intraventricular hemorrhage.*

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II. Hunt-Hess Scale: predicts outcomes, based on clinical presentation
III. Fisher Grade: risk of vasospasm, based on initial head CT

SYMPTOMS	H-H	CT FINDINGS	FISHER
Asymptomatic, mild HA, slight nuchal rigidity	1	No clot visualized	1
Mod-severe HA, no deficit except CN palsy	2	<1mm thick diffuse SAH blood	2
Drowsiness/confusion, focal deficit	3	>1mm thick blood or clot	3
Stupor, mod-severe hemiparesis	4	IVH/IPH extension w/ SAH	4
Coma, decerebrate posturing	5		

DIAGNOSTICS

- 50-70% of patients have a sentinel hemorrhage that is often misdiagnosed. Note that hemorrhage into the wall of an aneurysm may cause thunderclap headache in the absence of xanthochromia. Therefore, pts with a strong clinical suspicion despite negative CT and LP should undergo non-invasive vascular imaging (e.g. CTA).
- CT has a sensitivity of 98-99% which decreases with time (after 12 hrs). If CT is negative for subarachnoid blood but suspicion is high, lumbar puncture is needed to confirm diagnosis and must be performed acutely. Xanthochromia is the most reliable and sensitive CSF parameter, but is not apparent until 2 hours after headache onset. It usually lasts about 2 weeks, and *unlike HCT sensitivity of xanthochromia for SAH increases after 12 hrs*. Once confirmed, 4-vessel angiography is indicated. The angiogram may be negative in cases of a thrombosed pouch, vasospasm, or compression of the aneurysm by the hematoma, in which case a repeat CTA is indicated at 1 week (discussed below).
- Rarely, a patient may have a spinal AVM which produced the SAH → angiogram the suspected area

MANAGEMENT

- Acute management is dependent on airway stabilization, blood pressure control (SBP <160), & anticoagulation reversal (if present)
- Primary objective is to locate aneurysm & secure it within 48 hours (coiling preferred to clipping) repeat CTA post-operative to confirm aneurysm is secure and no remnants remain
- Prevent complications and neurologic deterioration (discussed below)

COMPLICATIONS

1. Rebleeding
   - 4% in first day if unsecured, decreasing thereafter
   - 75% of rebleeds occur in the first 3 days, often due to incomplete or lack of coiling/clipping

2. Seizures (15-25% in the acute period, 15% develop permanent epilepsy)
   - In minimally responsive patients, cEEG monitoring should be considered for seizure & vasospasm detection
   - Use of prophylactic AEDs may be considered in the acute post-bleed period (keppra 500 BID)
   - However, long-term AED use is not recommended except in the cases of documented seizure, intracerebral hematoma, intractable hypertension, infarction or MCA aneurysmal rupture

3. Hydrocephalus (15-85%)

- Treat with EVD (however, precipitous drops in ICP may cause re-rupture of unsecured aneurysms) preferred to lumbar shunting
- Acute (first day)—usually obstructive from the clot
- Subacute (first week) or delayed—usually communicating

4. Delayed cerebral ischemia (DCI)
   - Vasospasm occurs angiographically in 60-70%, clinically in 33%
   - Occurs between days 4-21, peaks around PBD #7-10 (which is why we typically monitor with daily TCDs from PBD 4-14 during this period)
   - Prevent vasospasm-associated ischemia (NOT vasospasm!!) with oral nimodipine (60mg q4)
   - Simvastatin has no proven efficacy in DCI from recent phase 3 STASH trial (Lancet Neurol 2014)
   - If vasospasm detected, ensure no hypotension → intra-arterial CCBs → and lastly angioplasty vs. intraventricular nimodipine if vasospasm persists
   - Monitoring methods include:
     - TCDs: Lindegaard ratio (CoW arterial velocity/ipsilateral extracranial ICA velocity) > 3 *OR* single vessel velocity >200cm/s *OR* increase of 50cm/s/day are suggestive of vasospasm
     - EEG: decreased alpha variability over suspected region supplied by vasospastic vessel
     - Confirm vasospasm with conventional angiography (can also use angiogram to intervene)

5. Hyponatremia (10-30%)
   - SIADH (normo/hypervolemic hypoNa): usually tx'd with fluid restriction (can be dangerous in setting of vasospasm)
   - Cerebral salt wasting (hypovolemic hypoNa): treat with salt tabs (2g q6), or fludrocortisone
   - Increases risk of vasospasm, CSW increases risk of poor neurologic outcome

6. Cardiac dysfunction
   - Most commonly due to myocardial stunning from catecholamine surge, but should rule out MI
   - T wave inversion, ST depression, QT prolongation, SVT, VT
   - Troponin I elevation (20-30% of cases): more common in severe H-H
   - RWMA and/or Takotsubo cardiomyopathy (8%): more common in women and severe H-H

7. General ICU complications
   - Fever (#1 complication): non-infectious (central) etiologies related to severity of SAH, independently associated w/ poor outcome
   - High risk of ventilator-associated PNA: prevent with oral chlorhexidine wash 5ml q4 (otherwise 1% risk per day); consider tracheostomy at day 14
   - High risk of DVT (15% cumulative risk, higher in patients with more severe H-H): start ppx when aneurysm secure or bleeding stable (~24hrs after admission) → weekly screening ultrasound increases likelihood of DVT detection but not PE prevention
   - High risk of sacral decubitus ulcer: q2 hr turning
   - Malnutrition: place NGT for meds if unable to swallow; PEG should be considered by day 14
   - Delirium/Pain: manage w/ antipsychotics, fentanyl boluses PRN

Unruptured Cerebral Aneurysms and Outpatient Considerations

Epidemiology

- SAH accounts for about 5% of all strokes worldwide, and most SAH are caused by aneurysms (80-85% of all non-traumatic SAH cases)
- The prevalence of intracranial saccular aneurysms is about 3 percent in the general

population, but this is increased with presence of specific risk factors.

-Risk factors for Aneurysm formation: Hereditary syndromes (Ehlers-Danlos, Marfan's, autosomal dominant PKD), family history (even without specific syndrome – prevalence in first degree relatives about twice that of general population), smoking, hypertension, estrogen deficiency (menopause), coarctation of aorta

- When rupture occurs, 10% of patients die before reaching hospital, and 30% of all patients will ultimately die

Aneurysm types

- Saccular: thin walled pouch like protrusions from intracranial arteries composed of thin/absent tunica media and absent internal elastic lamina
- Fusiform: enlargement or dilatation of entire circumference of arteria – can be formed due to athero
- Mycotic: related to infected emboli from endocarditis

-Most aneurysms are located in the anterior circulation (85%) -- junctions within the circle of Willis are particularly susceptible

-Saccular aneurysms are responsible for most SAH

Management

- Management largely hinges on risk of aneurysm rupture
- Data on the natural history of aneurysms is from two large prospective studies – the International Study of Unruptured Intracranial Aneurysms (ISUIA – US/Canada/Europe cohort) and the Unruptured Cerebral Aneurysms Study (UCAS – a Japanese cohort)
- Risk factors for Aneurysm rupture (can use PHASES score to calculate a 5 year rupture risk – see below)

1) Size: 7 mm and less have low risk
7-12 mm: 2.6% 5 yr rupture rate
13-24 mm: 14.5% 5 yr rupture rate
>25 mm: 40% 5 year rupture rate

2) Aneurysm growth: growth increases rate of rupture

3) Site: cavernous carotid artery aneurysms lowest risk, anterior circulation aneurysms intermediate risk, posterior circulation aneurysms highest risk. Data from ISUIA shows (reported as 5 yr rupture rates):
7-12 mm (cavernous carotid, anterior circulation, posterior circulation) -- 0, 2.6, 14.5%
13-24 mm: 3, 14.5, 18.4%
>25 mm: 6, 40, and 50%

4) Family history: familial aneurysms tend to rupture at smaller size/younger age

5) Prior aneurysmal rupture: probably increases risk of rupture from separate aneurysm, but this is not well quantified in studies

Predicting aneurysm rupture risk

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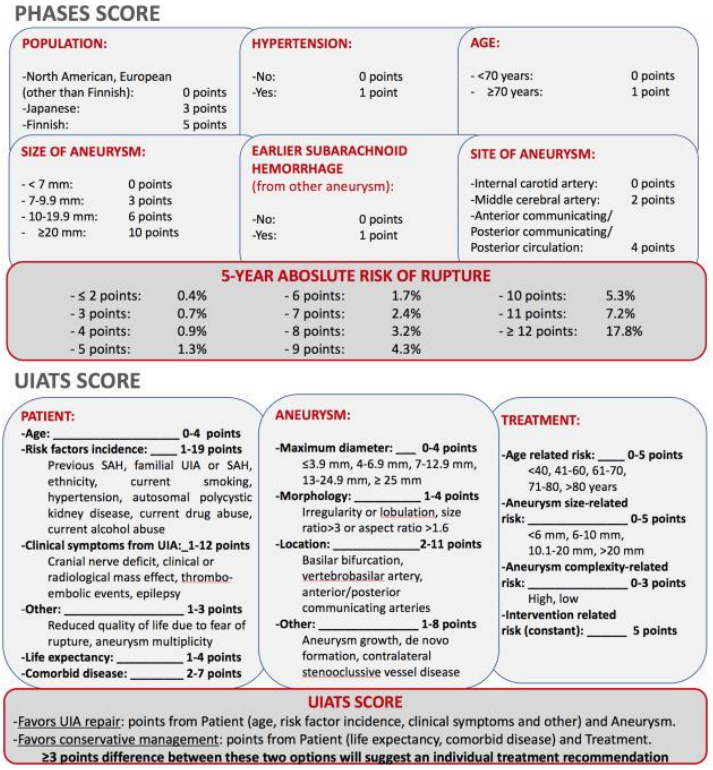


When to intervene

Guidelines from the Stroke Council of the American Heart Association (published prior to 2003 ISUIA data):

- The treatment of small incidental intracavernous internal carotid artery aneurysms is generally not indicated
- Coexisting or remaining aneurysms of all sizes in patients with an SAH due to another treated aneurysm warrant consideration for treatment
- Given the apparent low risk of hemorrhage from incidental, small (<7 mm) aneurysms in patients without previous SAH, observation rather than intervention is generally advocated. However, special consideration for treatment should be given to young (<50 years) patients in this group.
- Asymptomatic aneurysms ≥7 to 10 mm in diameter warrant strong consideration for treatment, taking into account patient age, existing medical and neurologic conditions, and relative risks for treatment

What are the options for intervention?

1)**Surgical placement of clip at neck of aneurysm** – risks associated with brain retraction, temporary arterial occlusion, and intraop hemorrhage

2)**Endovascular approach** to insert platinum coil into aneurysm lumen, forming clot that obliterates the sac – carries risk of intraprocedural rupture of aneurysm

-NOTE : coiling was previously reserved for smaller, saccular aneurysms with small necks and easy endovascular access, but now stent-assisted coiling can be performed

for large aneurysms with wide bases (the stent acts as a scaffold for the coil to occlude the aneurysm

What to do about AC/antiplatelets? No strong data shows an increase in rupture rate for patients treated with antiplatelets/anticoagulation, although antithrombotics can increase the severity of a rupture were it to happen.

Monitoring

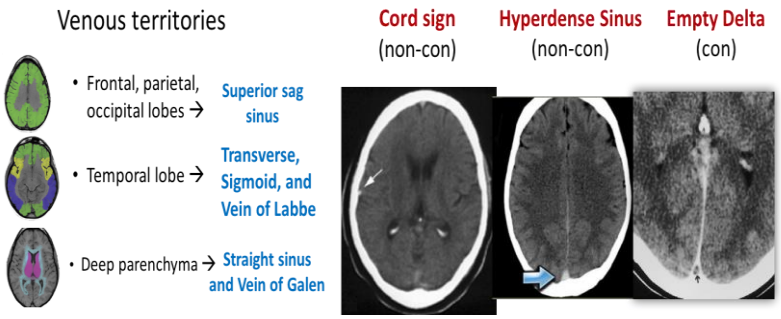
-CTA/MRA annually for 2-3 years, and every 2-5 years thereafter is aneurysm is clinically stable, although newly discovered small aneurysms can be initially re-imaged in 6 months due to increased risk of growth/rupture for newly formed aneurysms.

-FOR PREVIOUSLY TREATED ANEURYSMS that need follow up imaging, clipped aneurysms are better evaluated with CTA whereas coiled aneurysms are better imaged with MRA (some clips are also not MRI compatible).

CEREBRAL VENOUS SINUS THROMBOSIS

- Epidemiology
  - .5 –1 percent of strokes
  - Median age 37
  - Females/Males 3:1
- Risk Factors
  - Thrombophilia (genetic & acquired i.e. nephrotic syndrome, cancer), Drugs (OCPs)
  - Inflammatory disorders (vasculitis, IBD…), Infections (skull base eroding into sinuses), vascular malformations
  - Pregnancy and 4-8 weeks post-partum
- Presentation
  - Acute/Subacute presentation: symptoms can evolve over 48 hours
  - Elevated ICP
    - **Severe Headaches**, vision loss, papilledema, cranial nerve palsy, pulsatile tinnitus
  - Focal deficits: unilateral weakness, **seizures**
  - Encephalopathy
- Diagnosis
  - Bi-hemispheric involvement, infarcts cross arterial territories
  - CTH (only 30% CVTs seen)
    - Empty Delta Sign
    - Cord sign
  - CT Venogram
    - Empty delta sign
    - CTH/CTV as sensitive as MRI however cannot evaluate parenchyma nor acute ischemic changes
  - MRI/MRV: **Always add contrast when able.** Increases sensitivity
- Management
  - Heparin drip vs LMWH. No direct comparison, retrospective analysis suggests LMWH safer/more effective
  - Repeat imaging if clinically worsens/Consider IR consult for catheter directed clot retrieval
  - AC for 3 months-life time pending etiology
  - Consider Hypercoagulable workup (see appendix) and Malignancy workup if age>40

NEUROVASCULAR



ACUTE VESTIBULAR SYNDROME

- Severe sustained vertigo for days+ nausea/vomiting + spontaneous nystagmus + postural instability
- Main objectives in dealing with AVS:
  (1) Localize lesion centrally or peripherally to distinguish stroke (160,000-240,000) from vestibular neuronitis/labyrinthitis (150,000)

CENTRAL VERTIGO:
History suggestive of central cause:
- abrupt onset
- occipital headache (stroke) or neck pain (dissection)
- h/o trauma favors stroke (dissection)
- age > 50
- vascular risk factors OR stroke risk factors (A-fib, valve disease, etc.)

- *Exam* suggestive of central cause:
  - **abnormal HINTS battery with central findings OR a normal exam (technically a central pattern)**
  - only 50% of patients have abnormal general neurology exam: usually **truncal ataxia**

HINTS "plus" (Head Impulse, Nystagmus, Test of Skew, "plus" = hearing loss): >99% sensitive (>97% specific) for central vertigo
(1) Head Impulse (VOR): quick 15° rotation of head, ask pt to fixate on your nose
- Abnormal (refixation) = peripheral (note, includes AICA infarct)
- Normal oculocephalic response = central*

*most specific for central: you ***cannot*** have peripheral vertigo and preserved oculocephalic reflexes
(2) Nystagmus: direction-changing in lateral gaze = central [vertical & torsional nystagmus also central]
(3) Skew: vertical misalignment (re-fixation) on alternating eye cover-uncover test = central
(4) Hearing loss: ACUTE unilateral loss of hearing indicates unilateral cochlear nerve lesion (AICA)

Diagnostics (admit or observe overnight unless you're confident it's peripheral)
- CT in ED rules out cerebellar hemorrhage, then MRI brain (DWI only 88% sensitivity in first 2 days)
- CTA head/neck (vs. MRA w/ T1 fat sats if there is time) for dissection

NEUROVASCULAR

VESTIBULAR NEURONITIS

- Characterized by progressive vertigo worsening over several hours, peaks on day 1, then improves over next few days to weeks complete recovery takes weeks to months and is delayed by chronic Meclizine use
- Rarely do you get a great story for viral prodrome…but look for it!
- Exam: Abnormal oculocephalic reflex (head thrust) with movement towards the affected ear. Fast-beating mixed-torsional nystagmus away from the affected ear and does not change with direction of gaze. Nystagmus increases in intensity with gaze in direction of fast phase and decreases in intensity with gaze opposing direction of fast phase (Alexander's Law for all peripheral lesions).
- Treatment:
  (1) Steroids may help (10 day pred taper)
  (2) Other symptomatic treatments used in BPPV

RECURRENT VERTIGO SYNDROMES

BPPV - Benign Paroxysmal Positional Vertigo

- Characterized by vertigo provoked by head movement lasting < 2 minutes.
- Exam: Normal aside from Dix-Hallpike causing a mixed upbeating/torsional nystagmus toward the affected ear when it is down (patients w/ BPPV are also extremely nauseated and may in fact *vomit* on you).
- Nystagmus starts after a delay (10-40 seconds - this takes patience during the Dix-Hallpike!), then goes away after 30 seconds ("fatigues").
- Treatment:
  (1) Epley maneuver multiple times daily
  (2) Antihistamines: Meclizine (25-50 mg q6) x 1-3 days (longer may impair recovery)
  - Consider benzos alternatively: Valium 5-10 mg q12; Ativan 1-2 mg q8
  - Anti-emetics as needed
  (3) Vestibular rehab, consider referral to ENT

MENIERE DISEASE ("Endolymphatic hydrops")

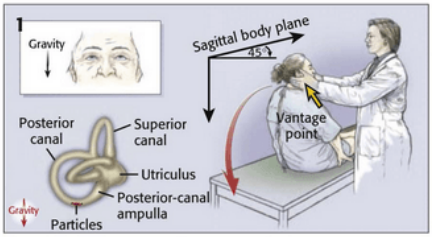
- Characterized by severe vertigo lasting for several hours, followed by several days of unsteady gait
- Presents in age 20-40 affecting 10-150 per 100k persons
- Triad of (1) episodic vertigo lasting <24 hrs, (2) sensorineural hearing loss (predominantly lower frequency that fluctuates and progresses over 8-10 yrs), and (3) tinnitus all 3 necessary for clinical diagnosis
- Acute treatment for vertigo in Meniere's disease is the same for BPPV w/ antihistamines
- Diuretics like HCTZ, acetazolamide, and betahistine are effective at long-term management

PERIPHERAL (75%)	**CENTRAL** (25%)
Vestibular neuronitis Meniere's Vestibular trauma/fistula Ototoxicity (aminoglycosides)* Vestibular migraine (3-5% prevalence) Zoster (Ramsey-Hunt)	Ischemic stroke (85% of central causes)** Cerebellar hemorrhage MS/demyelinating Drugs (AED's) Wernicke's Sarcoidosis

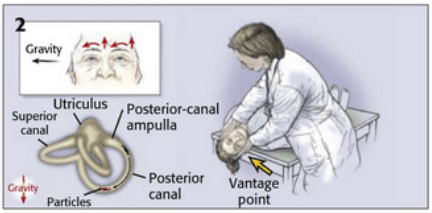
**Ototoxicity frequently causes bilateral peripheral vestibular disease, counteracting itself,*

therefore these patients typically do not have vertigo
*** 33% of strokes that cause dizziness are initially mis-diagnosed as peripheral*

DIX-HALLPIKE MANEUVER



The examiner stands at the patient's head, 45° to the right, to align the right posterior semicircular canal with the sagittal plane of the body.



The examiner moves the patient, whose eyes are open, from the seated to the supine, right-ear-down position and then extends the patient's neck slightly so that the chin is pointed slightly upward. The latency, duration, and direction of nystagmus, if present, and the latency and duration of vertigo, if present, should be noted. *Inset:* The arrows over the eyes depict the direction of nystagmus in patients with typical BPPV. The presumed location in the labyrinth of the free-floating debris thought to cause the disorder is also shown.

EXAM FINDINGS & MANEUVERS FOR THE DIZZY PATIENT

Spontaneous nystagmus: Observe the eyes for nystagmus with visual fixation and without (this is done with the Zee ophthalmoscope test - Pt covers one eye, examine the other with ophthalmoscope, blocking visual fixation. Can see retinal vein motion in opposite direction of nystagmus. Enhances subacute vestibular imbalance).

Gaze-evoked nystagmus: Pt gazes at a target 30□ left and right of center for 20 sec, observe for nystagmus. Eyes may drift midline with gradually decreasing velocity with fast refixation saccades in direction of gaze. Most normal people will have some nystagmus in far lateral gaze (end-gaze nystagmus). To distinguish pathologic gaze-evoked nystagmus from physiologic end-gaze nystagmus, look for amplitude greater than 4 degrees and asymmetry in right versus left gaze (pathologic features). Physiological nystagmus usually fatigues with prolonged gaze.

Saccades: Delayed saccades c/w *cortical or brainstem lesion*, overshoot c/w *vermal/fastigial cerebellar lesions*.

Oculocephalic reflex: The head thrust is as important as the Dix-Hallpike. Tell the patient to fixate on your nose, hold their head by the ears and move their head quickly and randomly from side to side (this has to be a fast and small but relatively forceful movement). Normal people with intact vestibular systems will maintain fixation on your nose. If the right vestibular system is dysfunctional, when you move the head quickly to the right, their eyes will deviate to the right with the head motion, and they will have a corrective saccade to the left back to your nose. If they have bilateral vestibular system dysfunction, i.e. gentamicin toxicity, they will have corrective saccades in both directions of head movement. Central lesions do not cause abnormal head thrust tests.

Fukuda step test (Unterberger test): Pt marches in place, eyes closed, arms extended. Positive if >45 deg turn in 50 steps. *Indicates labyrinthine dysfunction in the absence of cerebellar or prioprioceptive dysfunction.*

Romberg Test: While not primarily vestibular test, pt standing in tandem increases sensitivity for

vestibular lesions. Tend to fall towards side of lesion in both peripheral and central lesions. *In peripheral destructive lesions, pt will fall away from fast-phase of nystagmus; in central lesions, pt will fall towards fast-phase of nystagmus.*

Post-headshake nystagmus: Tilt head forward 30 deg and shake at 2hz for 20s, repeat this in horizontal and vertical planes. Fast-phase nystagmus toward the intact ear is c/w *peripheral lesion*; vertical nystagmus (cross-coupling) with horizonal head shake, prolonged nystagmus and dysconjugate nystagmus c/w *central lesion.*

Smooth pursuit (not exactly related to dizziness, but interesting): Watch the eyes following a moving target. Impaired pursuit suggests *ipsi parietal lobe damage.*

Outpatient Research Studies

See the Penn Stroke website (pennstroke.org, password silver9) for an up to date list of outpatient trials. Reproduced here is a summary of current clinical trials, which will be updated with each edition. Typically patients will be enrolled by the stroke fellow during their hospital stay, but somepatients may slip through the cracks.

If you think a clinic patient may qualify for one of these studies you can discuss with a stroke attending in clinic.

Aphasia research in Roy Hamilton Lab

Dr. Hamilton's lab performs a number of studies focused on the impact of non-invasive brain stimulation (transcranial magnetic stimulation and transcranial direct current stimulation) on recovering post stroke aphasia patients. If you are seeing a patient like this in clinic it is definitely worth reaching out to Dr. Hamilton's team to see if they would be a candidate for any studies!

- Daniela Sacchetti (contact by EPIC, Email or by phone at 215-573-8485)

Suggested Reading:

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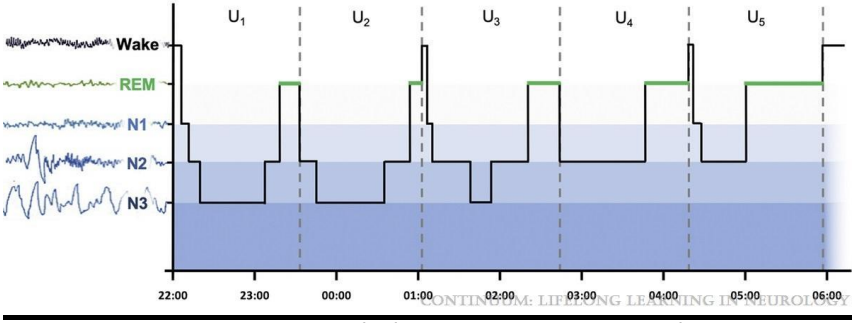
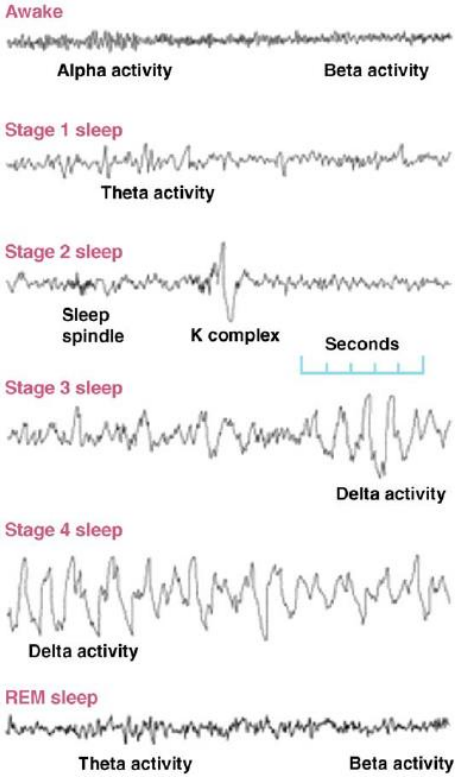
SLEEP

Sleep Architecture



From Neurobiology and Neuroprotective Benefits of Sleep,Schneider, Logan. CONTINUUM: Lifelong Learning in Neurology26(4):848-870, August 2020.

Schematic of normal sleep architecture across the sleep period



EEG features of different stages of sleep

SLEEP

The Polysomnogram/Sleep Study

The sleep study broadly refers to a test performed in the sleep lab or at home that measures various parameters through different stages of sleep. There are several different types of sleep studies that answer different questions, which are outlined below. In resident clinic, we will most often be ordering in house sleep studies. Interpreting sleep studies is not a routine part of residency, but if interested we can get exposure through sleep electives. **The sleep lab is located at 3701 Market Street and the phone number to schedule a sleep study is 866-912-7438.**

Types of sleep studies:

1) Polysomnogram: a comprehensive test performed overnight in the sleep center. Involves EEG + EMG to derive sleep stages (EMG leads placed on chin to assess for muscle atonia during REM sleep), and EKG, pulse ox. Airflow sensors can detect temperature changes in inspired/expired breath and can detect apneas, and nasal pressures transducers can also detect hypopneas. Belt sensors can determine respiratory effort in abdomen/thorax, which can differentiate central versus obstructive apneas. Limb electrodes can be placed on the tibialis anterior muscles to detect leg movement. Finally, body position can be recorded by a sleep technician/position monitors, which can be useful for OSA (can occur more in supine position).

**How to order "sleep study" – can be ordered with or without a consult to sleep medicine. Always order sleep studies WITH consult to sleep medicine, unless you staff with a sleep neurologist who tells you otherwise. For the consult order, you can list Drs. George, Bae, or Raizen if you prefer they been seen by a sleep neurologist).

2) Home sleep study: Alternative to polysomnogram when clinical question is focused on OSA and they do not have comorbid obesity, CHF, or COPD. No EEG data is recorded, but you will generally get measurements of airflow, pulse ox, heart rate, respiratory effort, and analysis of movement. Of note, severity of OSA may be underestimated by home sleep study as these devices may underestimate total sleep time due to lack of EEG. Therefore, the Apnea-Hypopnea Index (see OSA section) may be falsely low. As such, **when in doubt, order an in-house polysomnogram.**

**How to order. Choose "Home Sleep Apnea Test (Type 3)". Sleep center coordinators will help set this up.

3) Multiple sleep latency test (MSLT): subset of the polysomnogram and used in workup of hypersomnolence (including narcolepsy). Patient will complete a typical polysomnogram the night prior to make sure they are well rested (get at least 6 hours of sleep/exclude other sleep disorders like OSA). Then a couple hours after waking up, they get 4-5 nap opportunities occurring every 2 hours. They will get 20 minutes to fall asleep and if they fall asleep they will be woken up 15 minutes after sleep onset. Recording will be analyzed for mean sleep latentency time and for the presence of REM within 15 minutes of sleep onset.

- Make sure to order a UTox for that day as substance use can affect the results.
- In practice, these rarely are ordered in resident clinic. If you think your patient needs one of these, refer to sleep medicine.

  **How to order "sleep study w/ MSLT" – requires consult with sleep medicine

Obstructive Sleep Apnea

Background: characterized by repeated episodes of upper airway closure during sleep, leading to fragmented sleep and intermitted hypoxia. Most common symptoms are snoring, unrefreshing sleep, daytime sleepiness, nocturia, nocturnal awakening. Untreated OSA can increase risk for multiple medical issues like HTN, afib, stroke, diabetes. Obesity is main risk factor.

Screening: OSA is significantly underdiagnosed and screening is essential to help identify it, particularly high yield among headache and stroke patients in the neuro population. STOP-Bang is one useful screening tool (see below). It is designed for use in perioperative patients; a score of 3 or higher has an 84% sensitivity for predicting any OSA

- "Low," "intermediate," or "high" risk on STOP-Bang = risk for moderate/severe OSA
- Consider testing any of your patients with snoring/excessive daytime sleepiness for OSA even if they show up as low risk on STOP-BANG.

- Other symptoms to screen for: snoring, witnessed apneas, gasping, choking, coughing, heartburn, nocturia, palpitations from sleep, morning headaches, nocturnal diaphoresis.

STOP-Bang questionnaire

Please answer the following questions by checking "yes" or "no" for each one.

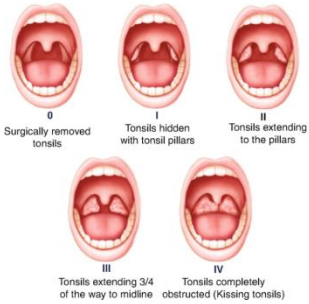
	Yes	No
Snoring (Do you snore loudly?)	❑	❑
Tiredness (Do you often feel tired, fatigued, or sleepy during the daytime?)	❑	❑
Observed Apnea (Has anyone observed that you stop breathing, or choke or gasp during your sleep?)	❑	❑
High Blood **P**ressure (Do you have or are you being treated for high blood pressure?)	❑	❑
BMI (Is your body mass index more than 35 kg per m^2?)	❑	❑
Age (Are you older than 50 years?)	❑	❑
Neck Circumference (Is your neck circumference greater than 40 cm [15.75 inches]?)	❑	❑
Gender (Are you male?)	❑	❑

Score 1 point for each positive response.

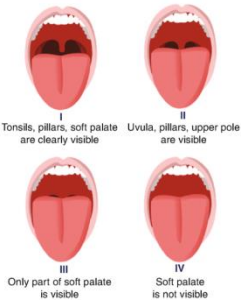
Scoring interpretation: 0 to 2 = low risk, 3 or 4 = intermediate risk, ≥5 = high risk.

Source: University Health Network, Toronto, Ontario, Canada (www.stopbang.ca/osa/screening/php). Used with permission from Sauk Prairie Healthcare.

Friedman Tonsils classification



Modified Mallampati classification



Diagnosis: Overnight polysomnogram in the sleep lab or a home sleep study (see above section).

Friedman tongue positions and the Modified Mallampati classification can be a quick bedside took to look for a crowded airway as part of your evaluation for referral to sleep clinic for OSA.

Terms

Apnea-Hypopnea index (AHI): the # of apnea and hypopnea events per monitoring time of sleep
Apnea = pause in breathing lasting 10 seconds with drop in O2 sat
Hypopnea = drop in airflow of 30%

Respiratory event index (REI): the # of apnea and hypopneas divided by total monitoring time

OSA criteria

- Mild OSA: AHI or REI ≥5 but <15 events/hr
- Moderate OSA: AHI or REI ≥15 but <30 events/hr
- Severe OSA: AHI ≥30 events/hr
- OSA syndrome: AHI or REI ≥5 with daytime sleepiness

Treatment options:

SLEEP

Table Treatment options for obstructive sleep apnea
Positive airway pressure (PAP)
Continuous PAP (CPAP)
Bi-level PAP
+/– Backup rate
+/– Average volume assured pressure support
Autotitrating PAP (may be CPAP or bi-level PAP)
Oral appliances
Tongue-retaining devices
Mandibular advancement devices
Surgical
Phase I (nasal, palatal, tongue)
Phase II (maxillomandibular advancement)
Hypoglossal nerve stimulation
Adjunct
Weight loss
Positional therapy
Nasal expiratory PAP
Noninvasive oral pressure therapy

CPAP is first line with variety of mask options – full face, nasal mask, nasal pillows…Greatest benefit is for those with severe OSA. CPAP is superior to oral appliances per many RTCs.

Oral appliances enlarge the upper airway/decrease upper airway collapsibility. Can be used in patients with mild-mod OSA who don't want CPAP, good dentition, BMI under 30. Can lead to 50% reduction in AHI.

Newer category is the hypoglossal nerve stimulator (Inspire). Requires ENT referral.

Insomnia

Background: defined as recurrent poor sleep quality/quantity causing distress/dysfunction…associated with older age, poor general health, decreased memory, mood, cognitive function…accounts for more than 5.5 million outpatient visits per year.

> **Acute insomnia:** symptoms of insomnia occurring < 4 weeks, generally caused by a precipitating event, illness, stress, new medication. May be managed with short term medication. Repeated episodes can evolve into a chronic insomnia and maladaptive behaviors can set in after 4 weeks.
> **Chronic insomnia:** symptoms of insomnia for at least 3 days a week for 3 months. Unlikely to spontaneously remit, requires behavioral modification.

Screening questions

- Bed time habits – time in bed, time taken to fall asleep after lights out (sleep latency), frequency and duration of awakenings, time out of bed in AM.
- Triggers for start of insomnia
- Lifestyle factors: caffeine use, exercise late in day, TV/screen time in bed, pets in bed, alcohol in evening, nicotine
- Consequences of poor sleep – fatigue, poor memory and mood, lack of energy, accidents from falling asleep
- Family history
- Assess for **delayed sleep phase disorder: has patient always just gone to bed much later and feels well rested if they are allowed to sleep in?**
- Co-morbid conditions: OSA, parasomnias, restless leg syndrome…

Treatment:
First line □ **cognitive behavioral therapy** consisting of behavioral interventions like sleep restriction, stimulus control, relaxation techniques and education (sleep hygiene) should be trialed first before reaching to medications (EFFECT SIZES = or > DRUGS). In-person or online methods can be effective. **One online resource: Cleveland Clinic Go To Sleep Online CBT program https://shop.clevelandclinicwellness.com/products/go-to-sleep-online**

Second line:Pharmacological treatments may be needed when CBT isn't enough:

Treatment (Basis of Recommendation)	AASM Recommendation	Quality of Evidence	AASM Benefits and Harm Assessment
Benzodiazepine receptor agonists			
Eszopiclone (based on trials of 2-mg and 3-mg doses)	An option for treatment of sleep-onset and sleep-maintenance insomnia (versus no treatment) in adults	Very low	Benefits outweigh harm
Zaleplon (based on trials of 10-mg doses)	An option for treatment of sleep-onset insomnia (versus no treatment) in adults	Low	Benefits outweigh harm
Zolpidem (based on trials of 10-mg doses)	An option for treatment of sleep-onset and sleep-maintenance insomnia (versus no treatment) in adults	Very low	Benefits outweigh harm
Orexin (hypocretin) receptor antagonist			
Suvorexant (based on trials of 10-mg, 15- to 20-mg, and 20-mg doses)	An option for treatment of sleep-maintenance insomnia (versus no treatment) in adults	Low	Benefits outweigh harm
Benzodiazepines			
Triazolam (based on trials of 0.25-mg doses)	An option for treatment of sleep-onset insomnia (versus no treatment) in adults	High	Benefits approximately equal to harm
Temazepam (based on trials of 15-mg doses)	An option for treatment of sleep-onset and sleep-maintenance insomnia (versus no treatment) in adults	Moderate	Benefits outweigh harm
Melatonin agonist			
Ramelteon (based on trials of 8-mg doses of ramelteon)	An option for treatment of sleep-onset insomnia (versus no treatment) in adults	Very low	Benefits outweigh harm
Heterocyclics			
Doxepin (based on trials of 3-mg and 6-mg doses)	An option for treatment of sleep-maintenance insomnia (versus no treatment) in adults	Low	Benefits outweigh harm
Trazodone (based on trials of 50-mg doses)	Not suggested as an option for treatment of sleep-onset or sleep-maintenance insomnia in adults	Moderate	Harm outweighs benefits
Anticonvulsant			
Tiagabine (based on trials of 4-mg doses)	Not suggested as an option for treatment of sleep-onset or sleep-maintenance insomnia in adults	Very low	Harm outweighs benefits
Over-the-counter preparations			
Diphenhydramine (based on trials of 50-mg doses)	Not suggested as an option for treatment of sleep-onset or sleep-maintenance insomnia in adults	Low	Benefits approximately equal to harm
Melatonin (based on trials of 2-mg doses)	Not suggested as an option for treatment of sleep-onset or sleep-maintenance insomnia in adults; melatonin may be used to help with circadian rhythm alignment	Very low	Benefits approximately equal to harm
L-tryptophan (based on trials of 250-mg doses)	Not suggested as an option for treatment of sleep-onset or sleep-maintenance insomnia in adults	High	Harm outweighs benefits
Valerian (based on trials of variable dosages of valerian and valerian-hops combination)	Not suggested as an option for treatment of sleep-onset or sleep-maintenance insomnia in adults	Low	Benefits approximately equal to harm

AASM = American Academy of Sleep Medicine.
[a] Modified with permission from Sateia MJ, et al. J Clin Sleep Med.[10] ©2017 American Academy of Sleep Medicine. ING IN NEUROLOGY

Sleep Related Movement Disorders

Non-REM parasomnias (i.e. disorders of arousal): consist of recurrent episodes of incomplete awakening from sleep. Examples include sleep walking, sleep terrors, and confusional arousals. Most often occur in first several hours of night as this is where slow wave sleep most often happens (N3).

	Disorders of Arousal	Nocturnal Seizures	Rapid Eye Movement Sleep Behavior Disorder
Age of onset	Usually childhood	Any age	Usually middle to older age
Time of night	Usually first third	Any time	Usually last third
Motor manifestations	Sitting up, screaming or confused, standing or walking	Clonic movements, orofacial and limb automatisms, dystonic posturing, hypermotor behaviors such as pelvic thrusting and bicycling	Screaming or shouting, punching or flailing, kicking
Stereotypy	No	Yes	No
Enuresis	No, except occasionally while sleepwalking	Yes, during generalized tonic-clonic seizures	No
Consciousness during events	Reduced	Reduced in seizures of temporal origin; may be preserved in seizures of frontal origin	Reduced
Recall of events	Reduced; little to no recall of dream content	Generally reduced, except for some frontal lobe seizures	May recall dream content if questioned immediately
Duration of events	Can last many minutes	Usually <1 minute	Can last many minutes
Polysomnogram	Sudden arousal from stage N3 sleep	EEG may show ictal (or interictal) activity but often not seen in frontal lobe seizures	Increased phasic or tonic muscle tone in rapid eye movement (REM) sleep

EEG = electroencephalography.

CONTINUUM: LIFELONG LEARNING IN NEUROLOGY

REM sleep behavior disorder (RBD): characterized by thrashing about during REM sleep – "dream re-enactment" often noticed by bed partner or patient may injure themselves…can be diagnosed on polysomnogram by demonstration of increased motor tone in chin/limbs during REM sleep…can be mimicked by OSA, periodic limb movements during non-REM sleep, nocturnal seizures.

NOTE: For either parasomnia, it's important to look for triggers, including sleep deprivation, caffeine, EtOH, OSA. If you treat these and it improves, could just be a secondary RBD.

Diagnosis: Sleep study that shows REM sleep without atonia. Ensure the patient is off melatonin at the time of the study.

Treatment focuses on reducing injury to patient/others. Bedroom should be modified and bed height should be lowered. Melatonin/Clonazepam are first line.

- Melatonin: 3-18mg. Decreases REM motor response and dream enactment behaviors. Side effects= abdominal discomfort, vivid dreams, sleep fragmentation. Rarely not tolerated.
- Clonazepam: 0.25-1mg, no effect on REM motor response but decreases dream enactment behaviors. Side effects= excessive daytime sleepiness, balance difficulties, falls, cognitive dysfunction. Commonly not tolerated (50%).

Risk of developing PD: high. A multicenter trial of 1280 patients showed that 74% developed parkinsonism after 12 years of follow-up, and another showed that 81% had a neurodegenerative disorder (PD or dementia) after 16 years.

Restless leg syndrome: uncomfortable urge to move the lower limbs along with abnormal sensations…strikes most often in the evening/night when patient is trying to get to sleep…5% prevalence that increases with age…may be seen with iron deficiency, depression, kidney failure, pregnancy, MS, neuropathy.
Diagnosis an be made clinically. Can be supported to PSG but not required. Use the following acronym: URGED— **U**rge to move legs often paired with unpleasant or uncomfortable sensations,

happens at **R**est, feels better when you **G**et up, tends to be more in the **E**vening, **D**dx doesn't sufficiently explain symptoms.
Test for ferritin, iron, transferrin sat, TIBC. Secondary tests: CBC, CMP, TSH.
Treatment

- Iron replacement if serum ferritin is less than 75 and transferrin sat is less than 20%.
    - if oral iron supplements are not helpful, can do IV iron supplementation
- Dopaminergic agents – Pramipexole, ropinirole, rotigotine. These can lead to augmentation (symptoms appear earlier in the evening after long term DA agent use)
- Gabapentin, opioids>>benzos if other agents are not effective

Narcolepsy/Hypersomnolence

Definitions:

- **Narcolepsy type 1** (narcolepsy with cataplexy): Excessive daytime sleepiness + cataplexy.
    - Cateplexy = sudden loss of muscle tone induced by emotion like laughter. Can be total and involve the entire body or partial and involve just neck/face/limb
- **Narcolepsy type 2:** excessive daytime sleepiness without cataplexy.
- **Idiopathic hypersomnia:** excessive daytime sleepiness with pronounced sleep inertia (extreme difficulty waking up) and long sleep periods (over 9 hours and with very long daytime naps).

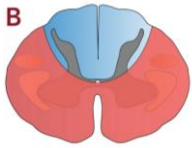
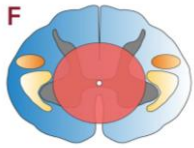
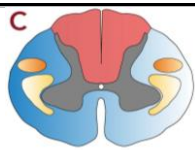
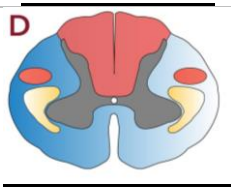
Please see chart on the following page for comparisons and diagnostic criteria.
Treatments: non pharmacological treatments typically do not work, so mainstay are medications to improve level of alertness. Note that these medications are better studied in narcolepsy and that is where they are FDA approved. They can also be used off label for individuals with idiopathic hypersomnia.

- Modafinil: enhances dopaminergic neurotransmission, usually taken BID, typically better tolerated than traditional stimulants
- Traditional stimulants like methylphenidate, amphetamine/dextroamphetamine
- Sodium oxybate: **Only FDA approved treatment for cataplexy, although venlafaxine/fluoxetine are also used**
- Solriamfetol: dopamine and norepi reuptake inhibitor
- Pitolisant: histamine H3 inverse agonist/antagonist that increases CNS histaminergic transmission and enhances wakefulness. Has been shown in trials to reduce cataplexy, but not yet approved by FDA for this indication

	Narcolepsy Type 1	Narcolepsy Type 2	Idiopathic Hypersomnia	Kleine-Levin Syndrome
Symptoms				
Excessive daytime sleepiness	Must be present	Must be present	Must be present	Must be present
Cataplexy	Common	Never	Never	Never
Sleep hallucinations	Common	Less common	Least common (but sometimes present)	Not typical
Sleep paralysis	Common	Less common	Least common (but sometimes present)	Not typical
Disrupted nocturnal sleep	Common	Less than narcolepsy type 1	Less than narcolepsy type 1, not typical	No
Long sleep times	Not typical	May be present	Common	Very prolonged during an episode
Pronounced sleep inertia	Rare	May be present	Common	Not typical between episodes
Diagnostic criteria (*International Classification of Sleep Disorders, Third Edition*)				
Multiple sleep latency test (MSLT) mean sleep latency for diagnosis	≤8 minutes	≤8 minutes	≤8 minutes	MSLT not necessary for diagnosis
Number of sleep-onset REM periods for diagnosis	2 or more	2 or more	0–1	MSLT not routinely used for diagnosis
Orexin (hypocretin) levels in CSF (if tested)	Low	Normal	Normal	Normal
Necessary criteria for diagnosis, in addition to excessive daytime sleepiness	(1) Cataplexy and typical MSLT findings *OR* (2) orexin (hypocretin) deficiency in CSF	(1) Typical MSLT findings *AND* (2) no other cause	(1) Typical MSLT findings *OR* (2) >11 hours sleep on 24-hour polysomnography *OR* (3) >11 hours sleep on average over at least 1 week of actigraphy, *AND* (4) no other cause	(1) Episodic sleepiness accompanied by cognitive dysfunction, altered perception, altered eating, or disinhibition *AND* (2) no other cause

CSF = cerebrospinal fluid.

SPINAL CORD DISORDERS

SPINAL CORD SYNDROMES		
Brown Sequard Syndrome - Hemicord process	**Clinical Presentation** - ipsilateral weakness - ipsilateral deficits in proprioception/vibration -contralateral pain and temperature deficits	**Anatomy** 
Anterior Cord Syndrome	- All motor function, pain/temp below level are impaired. - proprioception/vibration spared	
Central Cord Syndrome (usually 2/2 Syrinx, most often in the cervical cord)	Loss of b/l pain/temp in UEs LEs. ("Cape-like distribution"). As it expands, can get spinothalamic involvement medially laterally.	
Tabes Dorsalis (3^{O} syphilis) - dorsal column only	Loss of proprioception/vibration with spared pain/temp and strength.	
Subacute Combined Degeneration - dorsal column + corticospinal tract. - Think B12 , Cu, Vit E deficiency. - can also see similar pattern in HIV	Loss of proprioception/vibration, strength b/l, spared pain/temp.	

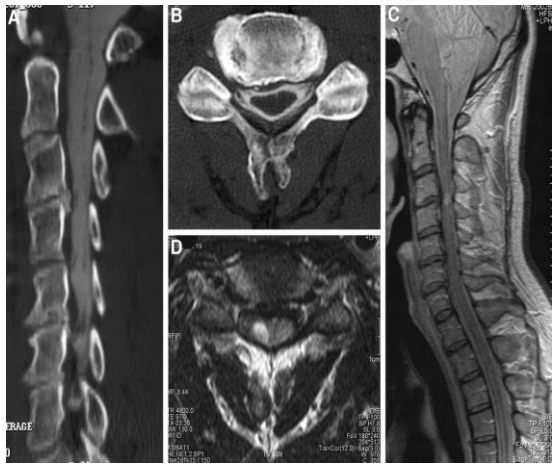
SPINAL CORD ISCHEMIA

- In the ED population, accounts for 1% of all strokes, but 5-8% of all myelopathies.
- 10% risk of SCI during aortic injury repair (e.g. TEVAR)
  - 6% had strokes so keep an eye out for that too.
- Other endovascular procedures have lower rates, but are still a major risk factor (e.g. bronchial artery or intercostal artery embolization; ECMO).
- Spinal cord ischemia can occur intraoperatively or after a delay (has been reported as far as 27 days post-op).
- Loss of SSEP (posterior cord) or MEP's (anterior cord) in the OR indicate ischemia and a cord at risk.
- Obviously consider alternative diagnoses (e.g. herniated disc, critical illness polyneuropathy, etc).
- Fun fact: risk of a spinal dural AVF is greatest among middle-aged men (dx often delayed by 12-18 mos). In these cases, the area of cord ischemia does not always sync up with the location of the fistula, so the entire spine is often imaged.

Table 1 Causes of Spinal Cord Ischemia

Vascular Compression
Local spinal column disease
Aortic manipulation
Endovascular procedures
Hypoperfusion
Systemic Hypotension
Local atherosclerotic lesions
Radiation therapy
Embolism
Thromboembolic disorders
Iatrogenic embolism
Fibrocartilaginous emboli
Prothrombotic Disorders
Meningitis
Vasculitis
Neoplasm

RISK FACTORS DURING AORTIC REPAIR
Advanced age
Aortic rupture
History of Stroke
Prior aortic surgery
Long cross-clamp time
Intra-operative hypotension
Sacrifice of intercostal vessels



VASCULAR ANATOMY

Anterior Spinal Artery

- Originates from vertebral aa. in cervical spine, supplies the anterior two thirds of the spinal cord, including the anterior horns, spinothalamic tracts, and corticospinal tracts
- Note that the ASA sends sulcal arteries to the deep portion of the white matter, which then branch either to the right or to the left
  - Loss of one sulcal artery can result in a unilateral ASA syndrome

Posterior Spinal Arteries

- Supply the posterior one third of the spinal cord, including the posterior commissure and dorsal columns

- Significant anastomosis between each other as well as a greater number of radicular arteries contributing to them, so they are more resistance to infarction than ASA
- Just like the brain, there are watershed regions in the spinal cord where ASA/PSA meet.

Artery of Ademkiewicz (The majority are left-sided; seen around T8-L3, most commonly at T10)
- Thoracolumbar vessel in 90% of patients which supplies majority of the lower T & L spine & conus.
- Makes a hairpin turn as it enters the cord.

PRESENTATION
- "We want McGarvey"
- Questions to ask:
  - What happened in the OR (prolonged hypotension, circ arrest, type of surgery)?
  - Did they lose SSEP's or MEP's? If so, was it transient or not?
  - What was their exam post-op?
  - Were they hypotensive with the onset of weakness?
  - Do they have a lumbar drain? Do they have an epidural catheter?
  - Was the onset with starting the epidural?
- Typical sx: Acute weakness, urinary retention, pain w/ clinical nadir at 12 hours after ischemic event
  - **NOT ALL SCI PRESENTS AS CLASSIC CORD SYNDROMES:** incomplete and delayed ischemia is not uncommon. May present with unilateral weakness due to intercostal spinal artery anatomy/watershed regions in relation to motor pathway anatomy

- Suggestive of spinal cord ischemia: Loss of SSEP's/MEP's, hypotension with onset, partial or no sensory loss
- Suggestive of an epidural complication: Onset with epidural placement, total sensory loss or sensory>>motor loss
- ASIA Impairment Scale
  - A: Complete loss of sensorimotor fxn
  - B: Only sensory fxn preserved
  - C: Mild motor preservation w/ >half muscles scoring <3/5
  - D: Moderate motor preservation w/ >half muscles scoring >3/5
  - E: Intact sensorimotor fxn

OUTCOMES
- SCI carries poorest prognosis (half improve during variable follow-up periods).
- AVM outcome also not too great w/ likely progressive deterioration from ischemia or hemorrhage.
- Post-operative pts w/ dural AVF repair have a high rate of motor recovery (>80%) or stability (15%).

WORK-UP/MANAGEMENT

1. **If patient has had recent thoracic procedure, spinal cord ischemia/infarct is #1 ddx until proven otherwise**
2. **Obtain STAT CT spine to rule out hemorrhage; if this is negative proceed to empiric treatment. DO NOT WAIT FOR MRI (it is supplemental).**
3. **Support cord perfusion: BP augmentation and lumbar drain**

•Spinal cord perfusion pressure = the difference between MAP and intraspinal canal pressure. Goal: Optimize perfusion of the cord by maximizing forward flow (MAP) and minimizing backpressure (lumbar drain).

•So can treat by increasing MAP >90 with vasopressors and reducing canal pressure in

the subarachnoid space (usually to 8-12 mm Hg) with a lumbar drain.

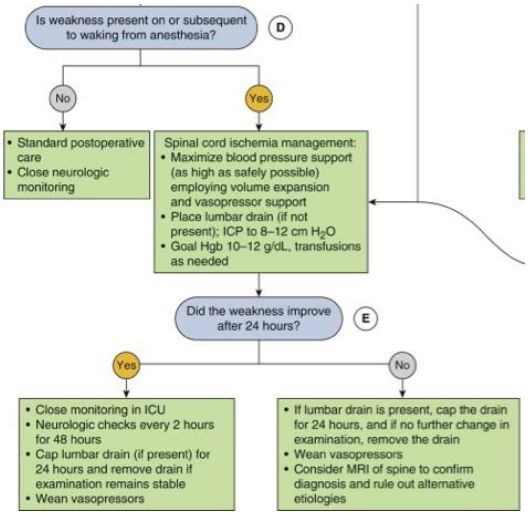
•Has not been evaluated in a controlled study for endovascular cases, but the temporal association of the intervention with observed improvement offers evidence of efficacy.

•Should be performed as expeditiously as possible to prevent secondary injury.

•If ischemia COMPLETE x 24 hours, unlikely to benefit (if only unilateral or mild weakness x 24 hours, can still benefit!!!)

4. **Improve oxygenation: In addition to addressing perfusion as above, also Hgb goal 10-12; transfuse as needed**

Pathway for management of spinal cord ischemia following aortic surgery



McGarvey, Michael. "Spinal Cord Infarction" ***Decision-Making in Adult Neurology*****. Edited by Brett Cucchiara and Raymond Price, Elsevier Inc, 2021. 47, pp. 98-99**

SPINAL CORD DISORDERS

ACUTE SPINAL CORD COMPRESSION

Unlike the brain, the cord rarely recovers function. Initiate treatment as soon as possible.

PRESENTATION

- Assume cord compression in any cancer pt with back pain.
- Consider if the pt has progressive neurological symptoms, including weakness/numbness (especially symmetric and without facial involvement) and bladder/bowel symptoms.
- Note general condition, vitals (ie, respiratory distress), back pain, history of trauma, known cancer or infection, duration of symptoms, recreational drug use, history of chronic steroid use (which can mimic cord compression).

EXAMINATION

- Note the vital signs (especially for respiratory distress, autonomic instability).
- Check for a sensory level.
- Check rectal exam (for saddle anesthesia, diminished rectal tone).
- DTRs may be diminished (ie, spinal shock) or hyperreflexic.
- Percuss the spine for tenderness.
- Note signs of rheumatoid arthritis which is associated with atlanto-occipital dislocation.

MANAGEMENT

-If trauma suspected, immobilize the neck (usually already done in the ED) and start IV methylprednisolone 30 mg/kg bolus over 15 minutes, then 5.4 mg/kg/hr over 23 hours.
-If tumor suspected, give IV Dexamethasone 20 mg bolus, then 10 mg q6.
-STAT MRI spine. Consider starting with plain films if there is a delay in getting an MRI, but the on-call Neurorads fellow should be made aware of the emergent need.
-STAT neurosurgical consult
Possibly hematology-oncology consult and XRT within 12 hrs if appropriate

Not usually admitted to the neurology service – think ICU, neurosurgery or oncology

Conus Medullaris vs. Cauda Equina Syndromes

	Conus medullaris syndrome	Cauda equina syndrome
Vertebral level	L1-L2	L2-sacrum
Spinal level	Sacral cord segment and roots	Lumbosacral nerve roots
Presentation	Sudden and bilateral	Gradual and unilateral
Radicular pain	Less severe	More severe
Low back pain	More	Less
Motor strength	Symmetrical, **less marked** hyperreflexic distal paresis of LL, fasciculation	More marked asymmetric areflexic paraplegia, atrophy more common
Reflexes	Ankle jerks affected	Both knee and ankle jerks affected
Sensory	Localized numbness to perianal area, symmetrical and bilateral	Localized numbness at saddle area, asymmetrical, unilateral
Sphincter dysfunction	Early urinary and fecal incontinence	Tend to present late
Impotence	Frequent	Less frequent

NOTES

APPENDIX A: SCALES & FORMULAE

Modified Rankin Scale

0—no symptoms
1—no significant disability despite symptoms: able to carry out all usual duties and activities
2—slight disability: unable to carry out all previous activities but able to look after own affairs without assistance
3—moderate disability: requiring some help but able to walk without assistance
4—moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5—severe disability: bedridden, incontinent and requiring constant nursing care

GLUCOCORTICOID COMPARISON

Drug	Equiv Dose (mg)	Rel anti-inflam potency	Rel mineralo activity	Duration (hrs)	Route
Cortisone	25.00	0.8	2	8-12	PO, IM
Hydrocortisone	20.00	1	2	8-12	PO, IM, IV
Prednisone	5	4	1	12-36	PO
Prednisolone	5	4	1	12-36	PO, IM, IV
Methylprednisolone	4	5	0	36-72	PO, IM, IV
Dexamethasone	0.75	30	0	36-72	PO, IV

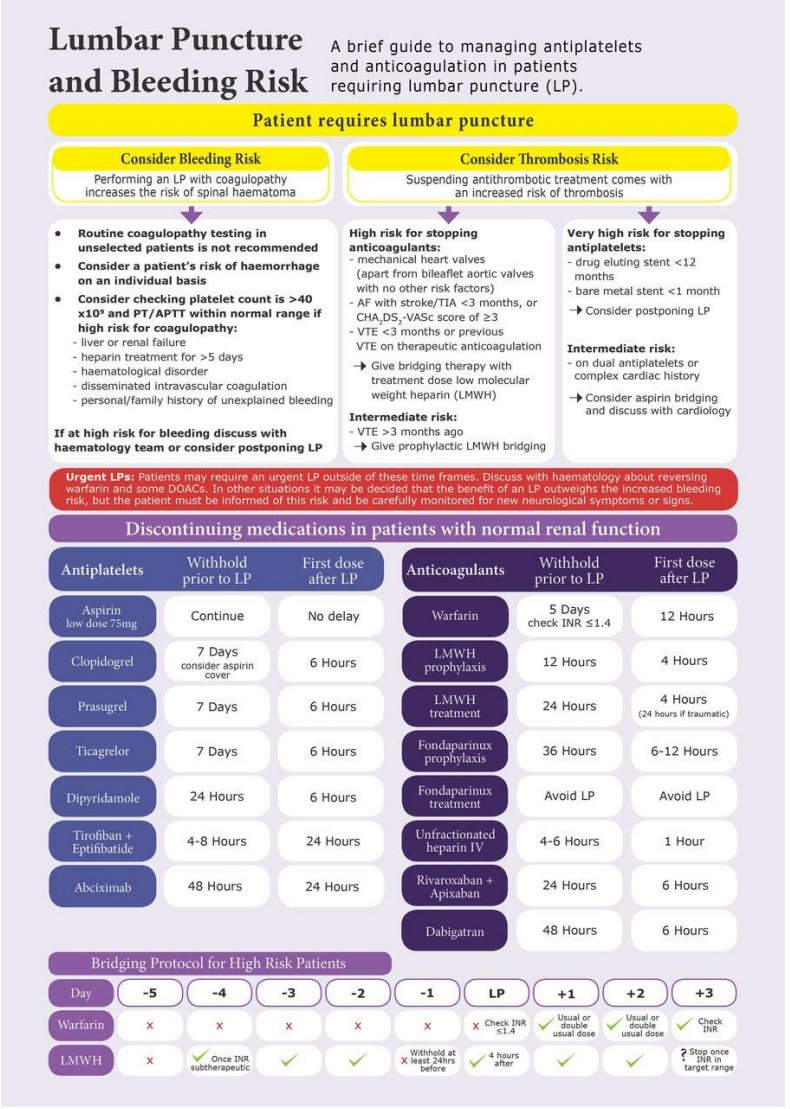
NARCOTIC COMPARISON

Generic	Trade	IM/IV	PO	Duration (hrs)
Codeine	---	120	200	4-6
Fentanyl	Sublimaze	0.1	---	1-2
Hydromorphone	Dilaudid	1.5	7.5	4-5
Meperidine	Demerol	75	300	2-4
Methadone	Dolophine	10	20	4-6
Morphine	Roxanol	10	60	3-7
Oxycodone	Percocet (+APAP)	15	60	4-6
Pentazocine	Talwin	30	150	2-3

APPENDIX B: LABORATORY TESTS

LUMBAR PUNCTURE

Contraindications: skin infection over puncture site, plt < 50K, INR>1.5, increased ICP w/ midline shift: get prior head CT in age>60, immunocompromised, h/o CNS disease, focal neuro exam including poor mental status



Lumbar Puncture and Bleeding Risk

A brief guide to managing antiplatelets and anticoagulation in patients requiring lumbar puncture (LP).

Patient requires lumbar puncture

Consider Bleeding Risk

Performing an LP with coagulopathy increases the risk of spinal haematoma

- **Routine coagulopathy testing in unselected patients is not recommended**
- **Consider a patient's risk of haemorrhage on an individual basis**
- **Consider checking platelet count is >40 x10⁹ and PT/APTT within normal range if high risk for coagulopathy:**
  - liver or renal failure
  - heparin treatment for >5 days
  - haematological disorder
  - disseminated intravascular coagulation
  - personal/family history of unexplained bleeding

If at high risk for bleeding discuss with haematology team or consider postponing LP

Consider Thrombosis Risk

Suspending antithrombotic treatment comes with an increased risk of thrombosis

High risk for stopping anticoagulants:
- mechanical heart valves (apart from bileaflet aortic valves with no other risk factors)
- AF with stroke/TIA <3 months, or CHA_2DS_2-VASc score of ≥3
- VTE <3 months or previous VTE on therapeutic anticoagulation

→ Give bridging therapy with treatment dose low molecular weight heparin (LMWH)

Intermediate risk:
- VTE >3 months ago

→ Give prophylactic LMWH bridging

Very high risk for stopping antiplatelets:
- drug eluting stent <12 months
- bare metal stent <1 month

→ Consider postponing LP

Intermediate risk:
- on dual antiplatelets or complex cardiac history

→ Consider aspirin bridging and discuss with cardiology

Urgent LPs: Patients may require an urgent LP outside of these time frames. Discuss with haematology about reversing warfarin and some DOACs. In other situations it may be decided that the benefit of an LP outweighs the increased bleeding risk, but the patient must be informed of this risk and be carefully monitored for new neurological symptoms or signs.

Discontinuing medications in patients with normal renal function

Antiplatelets	Withhold prior to LP	First dose after LP
Aspirin low dose 75mg	Continue	No delay
Clopidogrel	7 Days consider aspirin cover	6 Hours
Prasugrel	7 Days	6 Hours
Ticagrelor	7 Days	6 Hours
Dipyridamole	24 Hours	6 Hours
Tirofiban + Eptifibatide	4-8 Hours	24 Hours
Abciximab	48 Hours	24 Hours

Anticoagulants	Withhold prior to LP	First dose after LP
Warfarin	5 Days check INR ≤1.4	12 Hours
LMWH prophylaxis	12 Hours	4 Hours
LMWH treatment	24 Hours	4 Hours (24 hours if traumatic)
Fondaparinux prophylaxis	36 Hours	6-12 Hours
Fondaparinux treatment	Avoid LP	Avoid LP
Unfractionated heparin IV	4-6 Hours	1 Hour
Rivaroxaban + Apixaban	24 Hours	6 Hours
Dabigatran	48 Hours	6 Hours

Bridging Protocol for High Risk Patients

Day	-5	-4	-3	-2	-1	LP	+1	+2	+3
Warfarin	x	x	x	x	x	x Check INR ≤1.4	✓ Usual or double usual dose	✓ Usual or double usual dose	✓ Check INR
LMWH	x	✓ Once INR subtherapeutic	✓	✓	x Withhold at least 24hrs before	✓ 4 hours after	✓	✓	? Stop once INR in target range

Equipment checklist (before you put on the sterile gloves): consent, LP kit, gauze, extra sample containers, gloves, mask, chlorhexidine swabs, IV meds if needed, assistance holding the patient if needed

Sample destinations: all can be dropped off to the main lab on Founders 7, but if you don't trust transport…

oMicro: Gates 4, send a lot and ask them to hold extra so you can add on tests later

oImmunology (Cytology, flow cytometry – separate container for each): Founders 6, closes at 5pm, not open on weekends, useless on an old sample unless you add special reagent (rumor has it 1:1 mix with alcohol) immediately after collecting. Highest yield early in AM. Collect extra sterile tube "tube 5" for highest yield and lowest

contamination. Deliver directly to cytology lab. If c/f lyphoma, collect additional tube for flow.

oParaneoplastic ordered through HUP lab. If unusual syndrome or unexpected result, can send to Dr. Lancaster for further screening testing.

o14-3-3/RTQuic: See Cognitive section for details on ordering

Opening pressure: measured in the lateral decubitus position w/ legs straightened (bent legs can falsely elevate it)

oNormal: 11 cm H2O in infants, 15 cm H2O in children, 18 cm H2O in adults and 25 cm H2O in obese adults

oLow values usually due to prior LP and can be seen in spontaneous dural tears

oHigh values due to hydrocephalus, idiopathic intracranial hypertension (i.e. pseudotumor), cryptococcal meningitis.

Interpreting results

Protein: increased by 1 mg/dL for every 1000 RBCs

oIsolated increase is a nonspecific abnormality seen in any process that disrupts the blood-brain barrier (e.g. diabetes complicated by cerebrovascular disease and aging itself)

oIncreased without a corresponding elevation in cell count is *Albumino-cytologic dissociation*. This is the classic picture of Guillain-Barre.

oSuper high protein (in the 2 – 3 gram range) occurs in states of very low CSF flow with partial obstruction, often due to tumor

Glucose: should be about 2/3 of that in blood

oLow values (*Hypoglycorrhachia*) are never good. Possibilities include tumor, bacterial meningitis, some fungal meningitis and sarcoidosis.

Cell count: Send the first and last tubes. RBCs will decrease between the two in traumatic taps, but remain high if there are really RBCs in the CSF. Determine the true number of CSF WBCs by subtracting 1 WBC for every 700 RBCs (assuming normal serum WBCs). Cells disintegrate in CSF that sits around for more than 4 hours before laboratory analysis, resulting in '*pseudonormalization*' of CSF.

Micro: each test takes about 1cc of CSF. Many tests require approval. A good technique is to send a large sample to the lab and add on tests as necessary/approved.

obeware of possible false positive VDRL and EBV PCR and false negative HSV PCR if tap is traumatic

-HSV and VZV ab encephalitis testing needs to be compared with serum. Serum: CSF ratio of less than 20 suggests intrathecal synthesis of antibodies. HSV/VZR PCR may be negative after 1 week in acute infection thus always pair CSF PCRs with CSF IgM

oPCR testing should be done for suspected HSV1 and HSV2 DNA. (HSV2 can reactivate with fever and may be detected by PCR in the CSF of patients with other etiologies for encephalitis), also useful for VZV, enteroviruses, HIV-1 RNA, EBV DNA (seen in primary CNS lymphoma in HIV patients), West Nile virus DNA, CMV DNA, JC virus, and HHV-6 DNA. PCR is not useful for Lyme.

oIntrathecal anti-borrelial antibody is currently the best test for CNS Lyme testing.

oLatex particle agglutination tests are available for many bacterial antigens: Neisseria, Streptococcus pneumoniae, H. influenzae type B, group B streptococci and E. coli -this is useful for rapid diagnosis in patients who have been pretreated and whose Gram stain and cultures are negative. These tests are highly specific and can be done within one hour, but they are not highly sensitive. A negative test does not exclude infection

oNo rapidly available PCR exists for bacterial DNA

oCryptococcal antigen testing is highly specific, sensitive and fast.

Other Studies

o14-3-3 immunoassay for Creutzfeldt-Jakob disease can be falsely positive in HSV encephalitis, tuberculous meningitis and degenerative disorders. It should be interpreted in light of clinical symptoms and EEG abnormalities

oCSF protein electropheresis (includes oligoclonal bands): done for suspected MS. Requires same-day serum protein electropheresis or the lab will not run the CSF test. Bands are not specific for MS.

Guidelines to avoid panic

oDon't panic when you see grossly bloody CSF, you haven't penetrated the aorta (unless the blood is spurting out Monty Python style then it's probably okay to panic). Send tubes 1 and 4 for cell count.

Reference "LAB TEST SERVICES GUIDE" through UPHS intranet for updated information on sample volumes, containers needed, and lab requisition forms.

CSF Collection Tip Sheet

1. Order all tests in EPIC as STAT. This will ensure all your labels print
2. Include additional dedicated sterile urine cup(s) for cytology and flow cytometry, if applicable
3. Ensure you are collecting tubes 1-4 from the LP kit in order (tube numbers are physically etched on the tubes)
4. Place the MEDIUM SIZE order labels on the tubes/cups as follows:
    - **Tube 1:** Cell count 1
    - **Tube 2:** Protein/glucose
    - **Tube 3:** Micro/culture
    - **Tube 4:** Cell count 4
    - **Sterile urine cup 1 (if applicable):** Cytology or flow cytometry
    - **Sterile urine cup 2 (if applicable):** Cytology or flow cytometry
5. Place the tubes/cups in a biohazard transport bag and **place additional testing labels in the bag**
6. Ensure you have a **label** present for **EVERY test** ordered
7. Deliver to Central Receiving on Pavilion 3 Campus or via P tube to station 01

Minimum sample volumes (try your best to follow these guidelines or you may have to try the LP yet again)

Test	Volume	Verified	Hold time for extra sample	Performing Lab Location
Cytology	at least 1mL	Yes	1 week, 4 C	AP, 6 Founders
Protein and glucose	1.0 mL			AutoLab, 7 Founders
Flow cytometry	at least 2-5 mL			Flow Lab, 7 Founders
Cell Counts	2.0 mL			Heme, 7 Founders, PAV 3 lab
VDRL	0.5 mL	Yes	1 month, Frozen	Immunology lab, 7 Founders

Lyme Ab	2.0 mL	Yes	1 month, Frozen	Immunology lab, 7 Founders
NMDA-CSF	0.5-1.0 mL	Yes	2 months, Frozen	Immunology lab, 7 Founders
GAD65-CSF	0.5-1.0 mL	Yes	2 months, Frozen	Immunology lab, 7 Founders
Toxoplasma IgG Ab Elisa-CSF	0.5 mL	Yes	1 month, frozen	Immunology lab, 7 Founders
Routine, fungal, anaerobe, CrAG	at least 2mL	Yes		Micro, 4 Gates
AFB	5-10 mL	Yes		Micro, 4 Gates
HSV, VZV PCR (in house)	0.5 mL	Yes	2 weeks, frozen	Micro, 4 Gates
Enterovirus	0.5 mL/per PCR	Yes	2 weeks, frozen	Sendout, 4 Gates
EBV	0.5 mL/per PCR	Yes	2 weeks, frozen	Sendout, 4 Gates
HHV-6	0.5 mL/per PCR	Yes	2 weeks, frozen	Sendout, 4 Gates
JC	0.5 mL/per PCR	Yes	2 weeks, frozen	Sendout, 4 Gates
CMV	0.5 mL/per PCR	Yes	2 weeks, frozen	Sendout, 4 Gates
Other Pathogen PCR (send out)	0.5 mL/per PCR	Yes	2 weeks, frozen	Sendout, 4 Gates
Powassan (CDC send-out)	1 mL	Yes	2 weeks, frozen	Sendout, 4 Gates
Metagenomics	1 mL	Yes	3 weeks	Sendout, 7 Founders
Paraneoplastic Panel-Mayo	2-4 mL	Yes	3 weeks	Sendout, 7 Founders
Arbovirus	2.5 mL	Yes	2 weeks, frozen	Sendout, 7 Founders
14-3-3/RT Quic	2-5mL	Yes	3 weeks	Sendout, 7 Founders
oligoclonal bands	1.5 mL	Yes	3 weeks	Sendout, 7 Founders
NMO	0.5 mL	Yes	3 weeks	Sendout, 7 Founders
MOG	1.0 mL	Yes	3 weeks	Sendout, 7 Founders

Autoimmune Encephalitis Evaluation	0.5-1.0 mL	Yes	2 months, Frozen	Sendout, 7 Founders
VZV IgG/IgM	0.5 mL	Yes	3 weeks	Sendout, 7 Founders
CSF IgG Index	0.5-1 mL	Yes	3 weeks	Sendout, 7 Founders
Paraneoplastic Screen-ARUP	0.75-2 mL	Yes	3 weeks	Sendout, 7 Founders

SEROLOGY
Hypercoagulable evaluation
[] factor V Leiden, prothrombin 20210 gene mutation
[] anti-thrombin III
[] protein C and S (have to wait 2 weeks after acute event, and patient must be off AC x 1mo.)
[] antiphospholipid panel (anticardiolipin antibodies, lupus anticoagulant, DRVV, anti-β-2 glycoprotein IgG and IgM) if positive will need repeat in 12 weeks

Inflammogram
[] CSF: electropheresis (bands must be sent with SPEP, myelin basic protein), VDRL, JC virus PCR (if immunosuppressed)
[] Serum: SPEP, ANA, ANCA, SSA/B, ACE, RPR, Lyme ab, HIV, B12, ESR, TSH

APPENDIX C: IMAGING

APPROACH TO HCT

3 LIFE-THREATENING HCT FINDINGS
Blood where it doesn't belong: EDH, SDH, IPH, IVH, SAH
Midline shift: brainstem compression, herniation
Acute obstructive hydrocephalus

Houndsfield units:	
Bone	1000
Calcium	100
Acute blood	85
Tumor	30-60
Gray matter	35-40
White matter	25-30
CSF	0
Adipose	-100
Air	-1000

1. Big picture:
    [] asymmetry
    [] midline shift
2. Brain parenchyma:
    [] masses/edema (dark)
    [] early ischemia: deep gray nuclei, insular ribbon, gray-white differentiation, sulcal effacement, dense MCA
    [] if stroke: any hemorrhagic transformation?

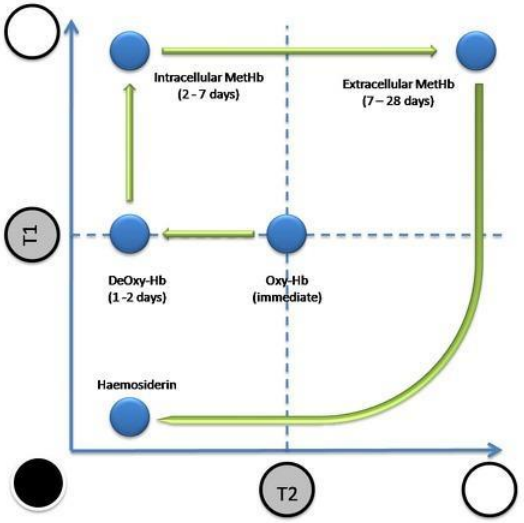
3. CSF system:
    [] hydrocephalus? (temporal horns)
    [] blood in ventricles? (occipital horns)
    [] patent basal cisterns? 3rd, sylvian fissures, inter-peduncular, ambient, aqueduct, 4th, pre-pontine
    [] foramen magnum
    [] sella
4. Extra-axial space:
    [] collections/hematomas (do sulci extent to skull?)
5. Orbits
6. Bone window
    [] skull fractures
    [] lytic lesions
    [] skull base and orbit
    [] sinuses

DATING ISCHEMIA ON MRI

SEQUENCE	DELAY TO ABNORMAL FINDINGS
DWI	Minutes (but variable first 6 hrs) --> lasts 10-14 days (T2 shine-through may persist)
ADC (dark)	Minutes (often precedes DWI) --> lasts 10-14 days (T2 shine-through may persist)
T2/FLAIR	Onset 6-12 hrs --> persists indefinitely
T1	Decreased parenchymal signal at 16 hrs --> persists indefinitely Laminar necrosis: Increased cortical signal at day 5-14 --> lasts 3 months
GAD	(1) Vascular enhancement at 2 hrs --> lasts 7 days (esp. incomplete infarcts) (2) Meningeal enhancement: large infarcts only, days 1-7 (3) Parenchymal enhancement at 7 days, lasts 2-3 months (if longer, consider other DDx)

DATING BLOOD ON MRI

TIME	T1	T2
0-24h	Dark	Bright
24h to 3-5d	Isodense	Dark
3-7d	Bright	Dark
1wk-month	Bright	Bright
2wk-yrs	Dark	Dark



RING EHANCING LESIONS (DDx: **MAGIC DR L**)
Metastases
Abscess
Glioma/GBM
Infarct (subacute)
Contusion
Demyelinating (incomplete ring)
Radiation necrosis
Lymphoma

RENAL GUIDELINES FOR GADOLINIUM

NOTE: I am still including these old guidelines, however***, there are now new gadolinium contrast agents called Macrocyclic agents that have essentially no risk for nephrogenic systemic fibrosis.***
Radiology will use this agent when there is an issue with the kidneys. You should still arrange to do contrast MRI scans in HD patients prior to their dialysis session, although the new agents are also safe in this population.

GFR > 50: okay

GFR 30 – 50: half dose
GFR < 30: no gad, at highest risk of nephrogenic systemic fibrosis (still only <3%)
- If gadolinium is necessary, may consider enhanced MRI in dialysis patients if the patient can be dialized immediately afterward (contact neuroradiology and renal to discuss study logistics)

Suggested Reading:
Allen LM, et al. Sequence-specific MR Imaging Findings That Are Useful in Dating Ischemic Stroke. Radiographics 2012;32:1285-1297.
Deo A, et al. Nephrogenic systemic fibrosis: A population study examining the relationship of disease development to gadolinium exposure. Clin J Am Soc
Nephrol 2007;2:264-267.

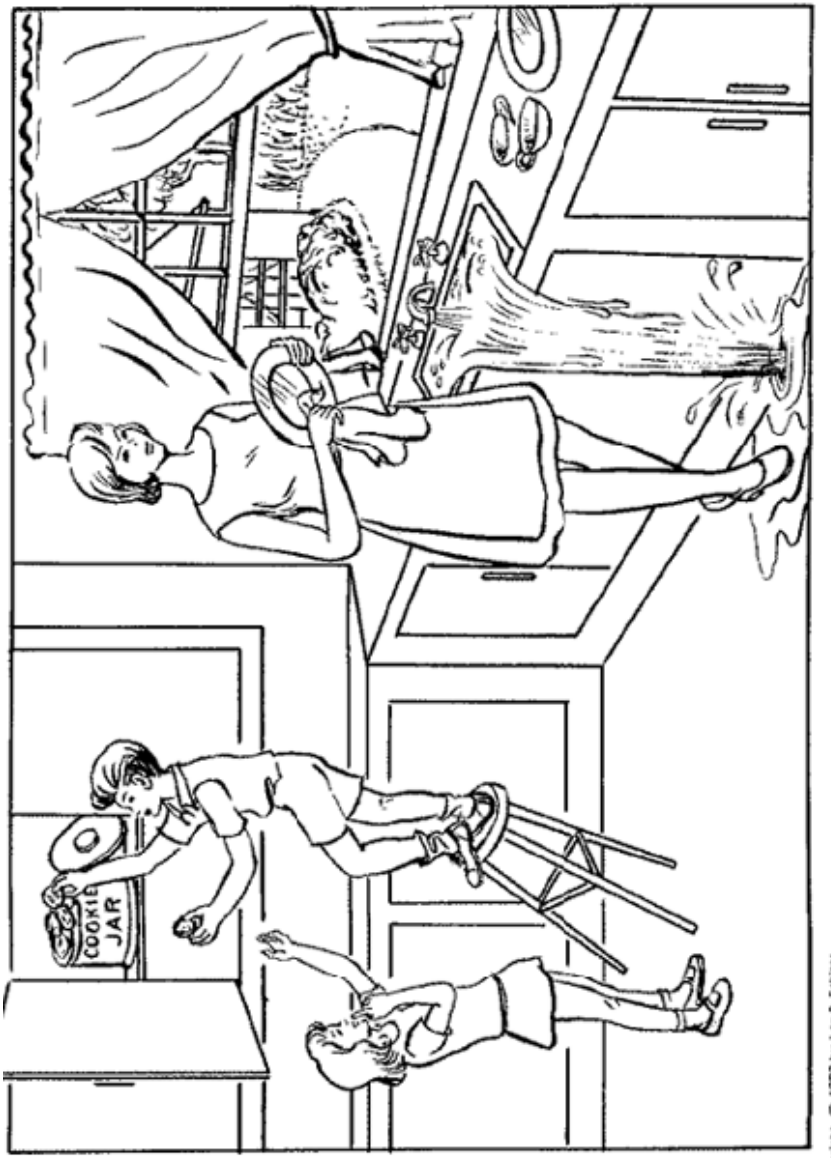
APPENDIX D: NIH STROKE SCALE (NIHSS)

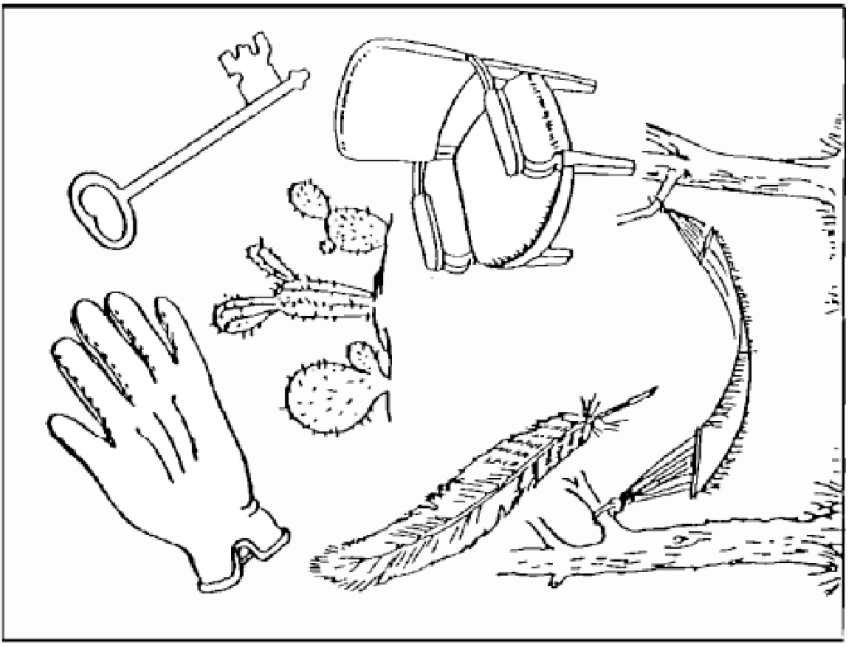
NOTES

Instructions	Scale Definition	Score
1a. **Level of Consciousness:**	0 = Alert; keenly responsive. 1 = Not alert, but arousable by minor stimulation to obey, answer, or respond. 2 = Not alert, requires repeated stimulation to attend, or in obtunded and requires strong or painful stimulation to make movements (not stereotyped). 3 = Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic.	_____
1 b. **LOC Questions:** The patient is asked the current month and his/her age.	0 = Answers both questions correctly. 1= Answers on question correctly. 2 = Answers neither question correctly.	_____
1 c. **LOC Commands:** The patient is asked to open and close the eyes and then to grip and release the nonparetic hand.	0 = Performs both tasks correctly. 1 = Performs one task correctly. 2 = Performs neither task correctly.	_____
2. **Best Gaze:** (Only horizontal eye movements are tested.)	0 = Normal 1 = Partial gaze palsy. This score is given when gaze is abnormal in one or both eyes, but where forced deviation or total gaze paresis are not present. 2 = Forced deviation, or total gaze paresis not overcome by the oculocephalic maneuver.	_____
3. **Visual:** Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate.	0 = No visual loss 1 = Partial hemianopia 2 = Complete hemianopia 3 = Bilateral hemianopia (blind including cortical blindness	_____
4. **Facial Palsy**: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes.	0 = Normal symmetrical movement 1= Minor paralysis (flattened nasolabial fold, asym smiling) 2 = Partial paralysis (total or near total paralysis lower face) 3 = Complete paralysis of one or both side (absence of facial movement in the upper and lower face)	_____

NOTES

Instructions	Scale Definition	Score
5 & 6. **Motor Arm and Leg:** The limb is placed in the appropriate position: extend the arms (palms Down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine).	0 = No drift, limb holds position for full 10 seconds. 1 = Drift, limb drifts down before full 10 seconds; does not hit bed or other support. 2 = Some effort against gravity, limb cannot get to or maintain elevated position, drifts down to bed, but has some effort against gravity. 3 = No effort against gravity, limb falls. 4 = No movement x = Amputation, joint fusion **5a. Left Arm** **5b. Right Arm** **6a. Left Leg** **6b. Right Leg**	_____ _____ _____ _____
7. **Limb Ataxia:** (This item is aimed at finding evidence of a unilateral cerebellar lesion.)	0 = Absent 1 = Present in one limb. 2 = Present in two limbs.	_____
8. **Sensory:** (Only sensory loss attributed to stroke is scored as abnormal)	0 = Normal; no sensory loss. 1 = Mild to moderate sensory loss 2 = Severe to total sensory loss; patient is not aware of being touched in the face, arm, and leg.	_____
9. **Best Language:**	0 = No aphasia, normal. 1 = Mild to moderate aphasia 2 = Severe aphasia 3 = Mute, global aphasia; no usable speech or auditory comprehension	_____
10. **Dysarthria:**	0 = Normal 1 = Mild to moderate; patient slurs at least some words and, at worst, can be understood with some difficulty. 2 = Severe; patients speech is so slurred as to be unintelligible in the absence of or out of proportion to any dysphasia, or is mute/anarthric. x = Intubated or other physical barrier	_____
11. **Extinction and Inattention:**	0 = No abnormality. 1 = Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities. 2 = Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognize own hand or orients to only one side of space.	_____
	TOTAL	


COOKIE
JAR
Copyright © 1983 by Lee & Felcher



You know how.

Down to earth.

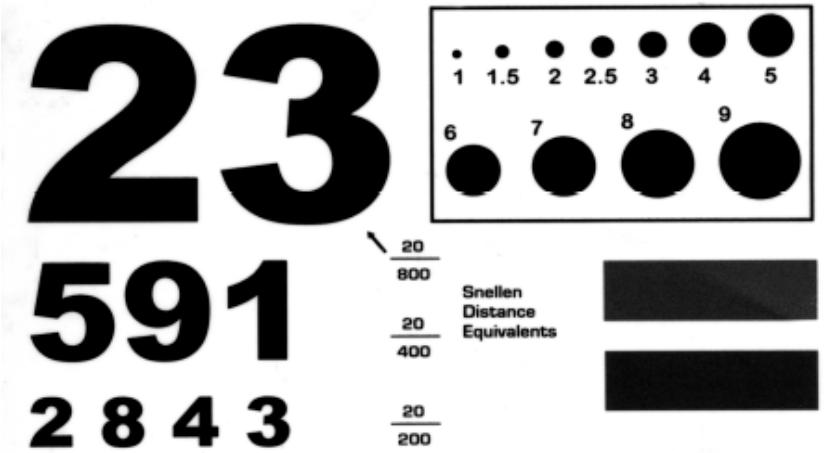
I got home from work.

Near the table in the dining room.

They heard him speak on the radio last night.

MAMA
TIP-TOP
FIFTY-FIFTY
THANKS
HUCKLEBERRY
BASEBALL PLAYER

APPENDIX E: NEAR VISION CARD



			POINT	JAEGER
4857	XOO	20/100	26	16
25396	OXO	20/70	10	7
824653	XOX	20/50	8	5
786542	OXO	20/40	6	3
927368	XXOX	20/30	5	2
428973	XOOX	20/25	4	1
739425	OOXX	20/20	3	1+

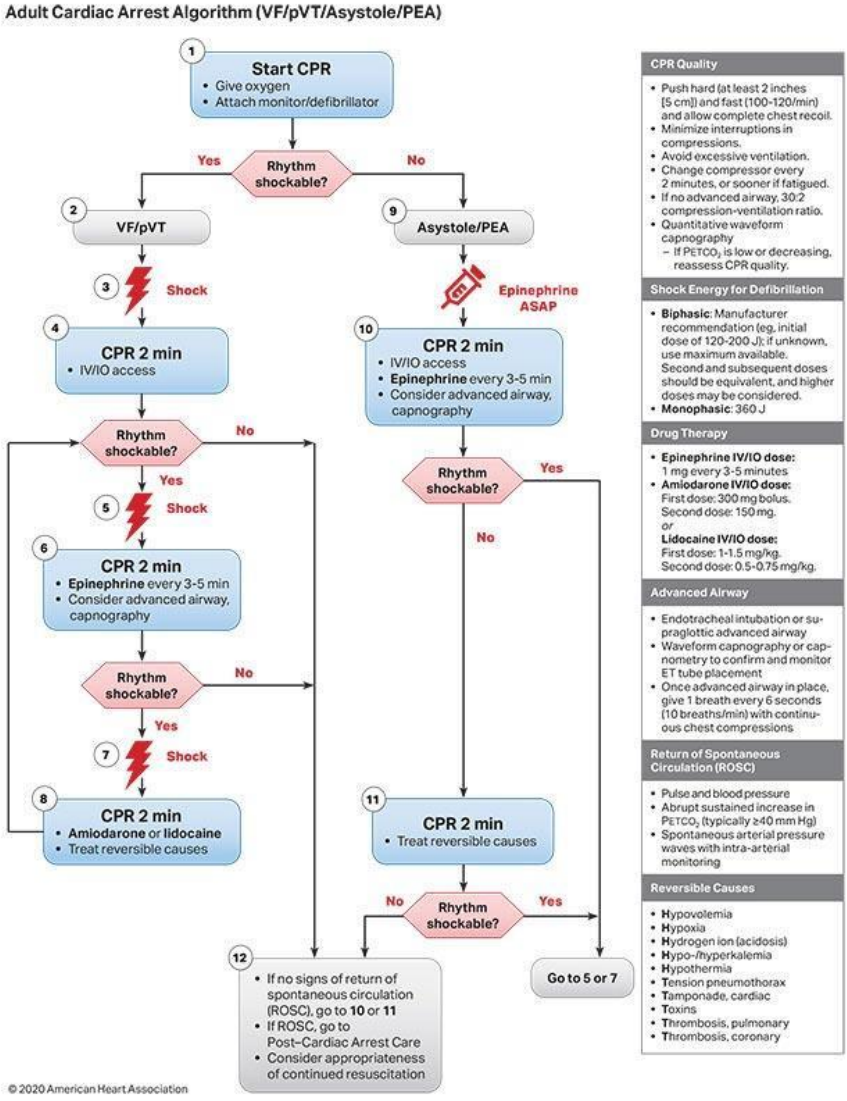
*** Hold card 14 inches from eyes. Good lighting.**
* Assess each eye individually and together, with and without glasses.
* Check myopes with glasses only. Presbyopic through bifocal segment.

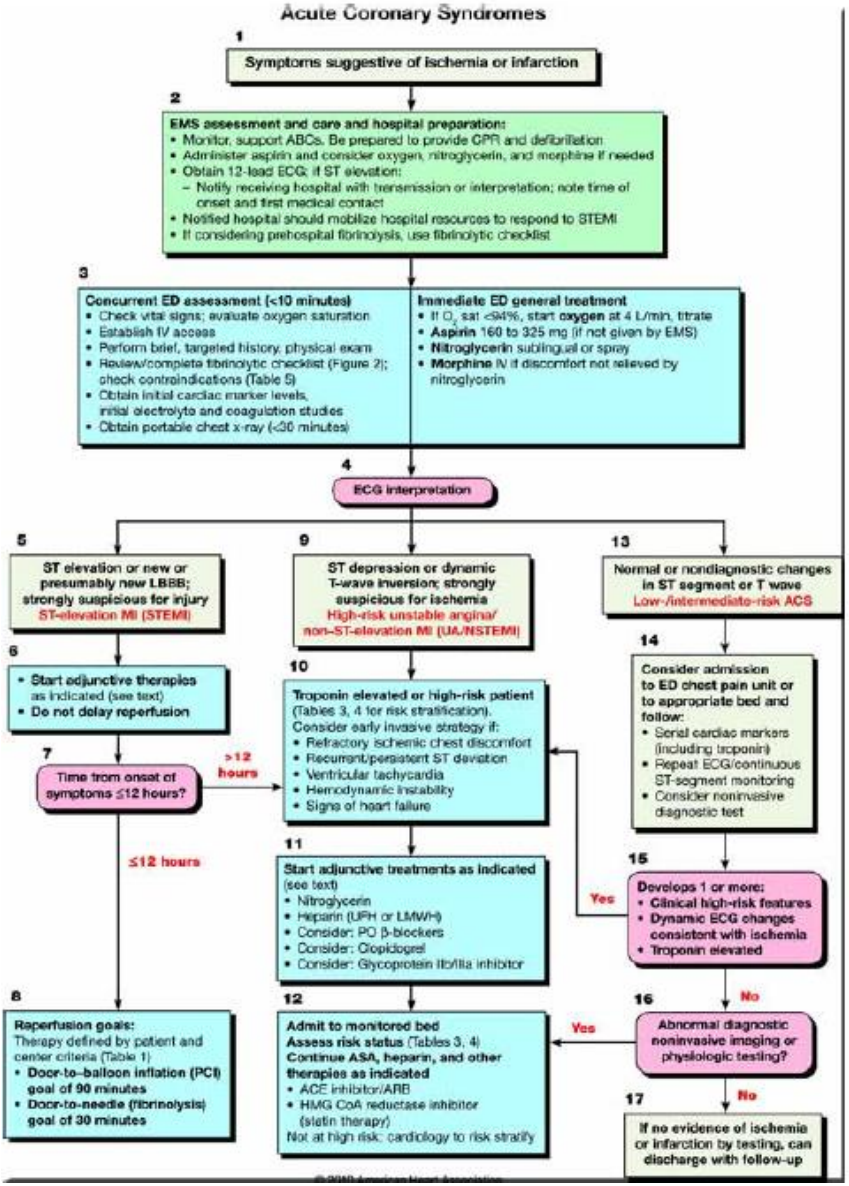
HEARING EXAM

HEARING (Cranial Nerve VIII, Acoustic):
Rinné's Test: Compares air and bone conduction (AC & BC). Tuning fork (512Hz) on the mastoid bone (test BC), when the sound is no longer perceived place the fork next to the ear (1 inch) to test AC. *Normally AC > BC.*
Weber's Test: Lateralization Test (bone conduction).
Place the handle of the tuning fork on the vertex, ask whether the sound is equally loud in both ears or louder in one side.
Schwabach's Test: Compares BC with normal observer.

Hearing	RINNE'S	WEBER'S
Normal	AC > BC bilaterally	midline
Conductive Loss	BC > AC affected ear AC > BC normal ear	lateralizes to affected ear
Sensorineural Loss	AC > BC both ears	lateralizes to normal ear

APPENDIX F: ACLS Algorithms




Acute Coronary Syndromes
1
Symptoms suggestive of ischemia or infarction
2
EMS assessment and care and hospital preparation:
• Monitor, support ABCs. Be prepared to provide CPR and defibrillation
• Administer aspirin and consider oxygen, nitroglycerin, and morphine if needed
• Obtain 12-lead ECG; if ST elevation:
– Notify receiving hospital with transmission or interpretation; note time of onset and first medical contact
• Notified hospital should mobilize hospital resources to respond to STEMI
• If considering prehospital fibrinolysis, use fibrinolytic checklist
3
Concurrent ED assessment (<10 minutes)
• Check vital signs; evaluate oxygen saturation
• Establish IV access
• Perform brief, targeted history, physical exam
• Review/complete fibrinolytic checklist (Figure 2); check contraindications (Table 5)
• Obtain initial cardiac marker levels, initial electrolyte and coagulation studies
• Obtain portable chest x-ray (<30 minutes)
Immediate ED general treatment
• If O_2 sat <94%, start oxygen at 4 L/min, titrate
• Aspirin 160 to 325 mg (if not given by EMS)
• Nitroglycerin sublingual or spray
• Morphine IV if discomfort not relieved by nitroglycerin
4
ECG interpretation
5
ST elevation or new or presumably new LBBB; strongly suspicious for injury
ST-elevation MI (STEMI)
6
• Start adjunctive therapies as indicated (see text)
• Do not delay reperfusion
7
Time from onset of symptoms ≤12 hours?
>12 hours
≤12 hours
8
Reperfusion goals:
Therapy defined by patient and center criteria (Table 1)
• Door-to-balloon inflation (PCI) goal of 90 minutes
• Door-to-needle (fibrinolysis) goal of 30 minutes
9
ST depression or dynamic T-wave inversion; strongly suspicious for ischemia
High-risk unstable angina/ non–ST-elevation MI (UA/NSTEMI)
10
Troponin elevated or high-risk patient (Tables 3, 4 for risk stratification). Consider early invasive strategy if:
• Refractory ischemic chest discomfort
• Recurrent/persistent ST deviation
• Ventricular tachycardia
• Hemodynamic instability
• Signs of heart failure
11
Start adjunctive treatments as indicated (see text)
• Nitroglycerin
• Heparin (UFH or LMWH)
• Consider: PO β-blockers
• Consider: Clopidogrel
• Consider: Glycoprotein IIb/IIIa inhibitor
12
Admit to monitored bed
Assess risk status (Tables 3, 4)
Continue ASA, heparin, and other therapies as indicated
• ACE inhibitor/ARB
• HMG CoA reductase inhibitor (statin therapy)
Not at high risk: cardiology to risk stratify
13
Normal or nondiagnostic changes in ST segment or T wave
Low-/intermediate-risk ACS
14
Consider admission to ED chest pain unit or to appropriate bed and follow:
• Serial cardiac markers (including troponin)
• Repeat ECG/continuous ST-segment monitoring
• Consider noninvasive diagnostic test
15
Develops 1 or more:
• Clinical high-risk features
• Dynamic ECG changes consistent with ischemia
• Troponin elevated
Yes
16
Abnormal diagnostic noninvasive imaging or physiologic testing?
Yes
No
17
If no evidence of ischemia or infarction by testing, can discharge with follow-up
No

DIRECTORY

PENNSYLVANIA HOSPITAL
From Outside: 215-829-xxxx
Pagers: 215-422-xxxx; from inside 2000-xxxx

GENERAL		CONSULT	
Main Number	215-829-3000	Anesthesia	(p) 1150/6165
Admissions	3321	Cardiology (PCA)	5064 (6055 for cath lab)
CODE (CRT)	5050	Dialysisinpt/Schiedt 5	(p) 5646
ED	3358/3244/3245/3920	Gastroenterology	(p) 5588
Heart Station/Echo	3348	General Surgery	(p) 6655
Medical Records	3931	ID	(p) 5752
Pharmacy	3246	Neurosurgery	(p) 6694
Physical Therapy	3258	Opthalmology	5311
Social Service	3508	Pain	(p) 0012/0022
Security	3434/8090	PICC	7713; (p) 0377
Security STAT	3333	Psychiatry	5233
Telemetry	5853	Pulmonary	(p) 5027
Wood Clinic	3521/5702/5771	Rad onc	3873
RADIOLOGY		Renal	8420
Neuro reading room	6668	Respiratory Therapy	(p) 1174
Spruce MRIscheduling	6741	Speech/ Swallow	715
CT/MRI scheduling	6686/8584	Urology	3409
Main Desk	3201	Vascular	(p) 1118
Daytime reading room	6004	**NEUROLOGY**	
Nuclear, V/Q scheduling	7272/3249	Office	6500
Nuc med reading room	5396	Fax	6606
Ultrasound scheduling	5399/6629	Consult pager	(p) 6200
Ultrasound reading room	6635/6629	Stroke pager	(p) 0702
On-call rad resident	(p) 6328	EEG/EP/Sleep	3250
General IR	5632; (p) 0107	EMG/NCV	6500/5634

NOTES

LABORATORY		EEG LTM tech (SMA)	(c) (610) 328-1166
Central	3552	Resident office	3085/3089
Blood bank	3218; (p) 5037	Ellen McPartland	3632; (c) (267) 266-0697
Chemistry	3551	**FLOORS**	
Cytology	3558/8035	NICU	8630/8294
Hematology	5043/5044/ 5045	CCU	8254
		4 Widener	3006
Micro	3555/5040	7 Cathcart	5769/3196
Serology	3546/5914	6 Cathcart	5767/5846/3221
Pathology	3544; (p) 5374	5 Cathcart	5765/5166
ABG	3860		

Other useful phone numbers to know:

- PAH MICU Resident Pager: 215-829-1116 (intern) or 1117 (senior)
- Critical Care Consult (daytime hours): Place a “IP CONSULT TO PULMONOLOGY” and call the MICU attending on call (on Qgenda).
- On- Call ICU Attending: MICU attending on call on Qgenda
- Hospitalist/Nocturnist: Place a “IP CONSULT TO HOSPITALIST” and contact hospitalist on call on Qgenda.
- RRT Nurse Coordinator: ask charge nurse to call, number available on every unit.

NOTES

HOSPITAL OF THE UNIVERSITY OF PENNSYLVANIA (see rolodoc also)

GENERAL		CONSULTS	
HUP Main Number	662-4000	Allergy & Immunology	page operator
Page Operator	**662-2222**	Anesthesia	908-0400
Admissions/Bed Mgmt	662-2335	Apheresis	215-847-6571
Drug Info	662-2903	Cardiology	page operator
Inpatient Pharmacy	662-2907, 2909	Dermatology	(day) (610) 734-6560 (night) 487-8527
Legal Affairs	662-2546	ENT	308-2170
Medical Affairs	662-2286	GI	page operator
Medical Records	662-3150	GYN/Ob	215-306-5777
Outpt. Pharmacy	662-2920	Hem-Onc	page operator
Patient Info	662-3308	ID	page operator
Physician Charting	662-3153	ID approval	215-306-0336
Security	662-2677	IVIG – Gene Gibson	(o) 349-8814, (c) 687-0163
Transfer Center	662-3555	Neuro-opthalmology	(p) 812-2869
Transport	662-2476, 2478	**Neurosurgery**	**(p) 312-3418, (c) 588-5488**
Utilization Review	662-3161	Nutrition	662-3285
Telecomm (Bob C)	662-2492	Ophthalmology	452-2339
LABS		Phlebotomy	812-1643
Central Receiving	**662-3475**	Physical Medicine/Rehab	page operator
Blood Bank	662-3448	PT/OT gym	662-3260
Blood Gas/Critical Care	662-3728, 3724	**PICC line**	290-5657
Chemistry	662-6788	Psychiatry	401-1155
Coags	662-3454	Pulmonary	page operator
Cytology/Cytopathology	215-487-8524/215-662-3209	Radiation Therapy	662-2428
Endocrine	662-4021/3420	Rheumatology	page operator
Flow cytometry	662-6023	Speech Therapy	662-3240
HIV Testing	662-4021	**FRIENDS AND NEIGHBORS**	
Serology/Immunology	662-6024	CHOP	590-1000
Micro	662-3415	CHOP Neurology	590-1719
Outpatient	662-2707	PRESBY	662-8000

NOTES

STAT	662-2510	SCHEIE EYE	662-8100
Toxicology	662-3474	RADNOR Clinic	(610) 902-2400
Syphilis hotline	685-6737	**CLINICS**	
RADIOLOGY		Brain Tumor	662-4485
Neuro reading room	**662-3480/1**	Cardiology	615-4949
ED reading room	662-7707	Dermatology	662-2737
X-ray/chest CT read room	662-3061	GI	662-3667
Body CT reading room	662-3142 (body doc)	GYN	662-2724
Head CT	662-3142	Immunodeficiency	662-2473
ED HCT/stat CT at night	662-3084	Medicine	662-2720
MRI scheduling	662-3000	Neurosurgery	662-3487
MRI tech	349-5596	Ophthalmology	662-6340
Founders MRI	349-5270	Otorhinolaryngology	662-2777
Devon MRI	349-5596	Renal	662-2638
Neuro angiogram	662-3064/3065	Rheumatology	662-2454
Neurovascular lab	662-3611	Sleep Center	662-7977
General ultrasound	662-3123	**FLOORS**	
X-ray tech	662-3011/6558/3017	EMU	349-8765
General IR	301-3076	S9	662-3807
PAC/Soutside scans	615-5929	S10	662-3817
Dr. Bob Hurst	961-6993	S11	662-3823
STUDIES		S12	662-3882
Echo	662-4624/615-4151	Ravdin 9	662-3821
TEE	615-4668	Rhoads 2NICU	662-3868
Echo reading room	662-2687	Rhoads 5 SICU	662-3852
Nuclear stress test	662-7285	F5 SICU	662-3841
Stress test reading room	662-7519	MICU	662-3880/3833/7195/7185
Nuclear Medicine	662-3076	CCU	662-3890/7193
Surgical Pathology	662-6526	CICU	662-3836/7191
Neuropathology	662-2967	ED	662-3920
Micro approval resident	960-6941	**SUPPLIES**	
Path approval resident	306-0286	Central supply	662-2904

Long Distance Code: dial full number followed by 68786 (identical procedure for faxing)

NOTES

NEUROLOGY ATTENDING PHONE LIST

Attending	Pager	Office	Cell	Secretary
Aguirre		662-3390	(267) 226-6695	Crystal Rich
Amado		662-3397	(215) 495-9730	Karen Conroy
Avery		349-8460	(215) 868-1193	Sherri Archer
Bar-Or		662-3606	(267) 591-0136	Grace Williamson
Berger		349-8304	(859) 492-8477	Gail Rogers
Bird	487-5288	662-6551	(610) 240-0565	Karen Conroy
Blum		662-8581	(267) 438-7572	
Brandstadter		662-3606	(215) 439-0190	Shakyra Gillard
Broderick		662-3606	(267) 624-4435	
Cantor	422-5361	662-7772	(610) 368-9941	
Chandler		615-0296	(215) 687-9527	
Chatterjee		662-3606	(215) 300-1044	Crystal Rich
Chen-Plotkin		829-6708	(617) 312-4114	
Conrad		615-2670/2671	(267) 760-7795	Vicki Lambritsios
Coslett	306-0913	615-3428	(215) 687-7550	Marilyn Ramos
Cristancho, D.		662-3606	(267) 455-3436	
Cucchiara		662-6738	(215) 593-6528	Justine Gallo
Dahodwala		829-3424	(267) 909-5539	
Davis		615-2670/2671	(609) 306-5746	Vicki Lambritsios
Deik		829-7512	(917) 653-9894	
Detre		349-8465	(610) 348-1154	Kim Sears
Diaz-Arrastia		662-9718	(214) 641-3086	Vincent Scordia
Do		615-3717	(267) 240-0262	Shana Miller
Douglas		662-3606	(267) 734-5446	
Ellis		615-2670/2671	(215) 301-9034	Vicki Lambritsios
Elman		829-8407	(610) 574-4208	
Favilla		615-3727	(215) 301-9736	Justine Gallo
Feinberg		829-7556	(215) 990-2961	
Fisher		662-3371	(610) 517-0680	Karen Conroy
Ganguly		615-2670/2671	(267) 760-7857	Vicki Lambritsios
Gelfand		615-2670/2671	(917) 748-4640	Vicki Lambritsios
George, D.		615-5067	(215) 776-0143	Kim Sears
Grossman		662-3361	(610) 506-0871	Crystal Rich
Gugger		615-2670-2671	(267) 624-4434	Vicki Lambritsios
Hamedani		349-8460	(919) 426-3595	Sherri Archer

NOTES

Hamilton, R.		662-4265	(215) 779-1603	Courtney Coulter
Humbert		662-3606	(267) 402-8219	
Ingala		(856) 427-4336	(301) 461-0584	
Irwin		662-3361	(215) 806-7935	Crystal Rich
Jacobs	404-4370	662-3647	(610) 608-1987	Gail Rogers
Jensen		662-3360	(617) 645-1790	Sonja Ogden
Joshi		615-2670/2671	(215) 279-0626	Vicki Lambritsios
Kaiser		614-0356	(215) 313-4597	Marilyn Ramos
Kalanuria		662-3363	(267) 438-9866	Justine Gallo
Karam		615-3751	(215) 906-1939	Karen Conroy
Kasner	452-4944	662-3564	(215) 593-6523	Kim Sears
Kerson		(610) 279-7443	(610) 331-2117	
Kolson	306-5136	349-8146	(610) 544-5758	Ivone Santos
Khella		662-8870	(610) 613-2079	
Kimbaris		829-6500	(443) 812-4767	
Kumar		662-3396	(610) 986-1121	Kim Sears
Lancaster	314-0297	349-8032	(215) 200-7646	Shana Miller
Lasker		829-7512	(617) 835-2282	
Lawler		662-3371	(610) 291-3861	Marilyn Ramos
Levine		662-3368	(215) 756-1671	Kim Sears
Lewis		829-8593	(215) 964-5810	
Litt		615-2670/2671	(484) 343-0893	Vicki Lambritsios
Liu		349-8460	(610) 733-1363	Sherri Archer
Lynch		662-6556	(267) 584-5958	
Manning		662-3606	(508) 561-0345	
Markowitz		662-4521	(215) 694-0770	Gail Rogers
McGarvey		662-4892	(215) 475-2450	Justine Gallo
Mendlik		615-1533	(215) 240-0673	Crystal Rich
Messe		662-3363	(215) 593-6526	Justine Gallo
Michaels		662-3898	(716) 570-3260	
Narula		662-3606	(917) 664-2958	Shakrya Gillard
Novello		829-6500	(267) 586-0909	
Orthmann-Murphy		662-3606	(215) 900-7889	Shakyra Gillard
Ozudogru		662-3606	(385) 228-3707	
Perrone		662-3606	(215) 459-0405	
Price	265-3050	662-2625	(610) 608-4548	Karen Conroy
Pruitt	984-3557	662-2796	(609) 206-4931	Marilyn Ramos
Quinn		662-2625	(703) 283-7370	Karen Conroy
Raghupathi		615-2670/2671	(703) 597-7815	Vicki Lambritsios
Raizen		746-4809	(610) 716-5341	
Rothstein		662-3339	(267) 624-4442	Kim Sears

NOTES

Rubenstein		662-2630	(215) 416-5611	Crystal Rich
Samudralwar		662-3647	(215) 407-5082	Ivone Santos
Sandsmark		662-9718	(314) 583-0756	Vince Scordia
Scherer		349-5313	(610) 368-3597	Shana Miller
Schindler		662-3606	(267) 901-2901	
Shin		662-3898	(267) 734-3042	
Shindler		662-3606	(215) 783-6415	Shakyra Gillard
Sinha		662-3606	(848) 702-6182	
Sloane		662-3606	(267) 584-4641	
Spindler		829-6708	(732) 614-4547	
Stein		662-2614	(570) 778-3914	Kim Sears
Tamhankar		662-8042	(856) 304-9322	
Tran, B.		662-3371	(714) 487-8373	Karen Conroy
Tropea		829-6500	(267) 600-5545	
Vaishnavi		662-7810	(404) 394-0744	
Vaswani		829-6500	(410) 929-4728	
Vijayaraghavan		662-8570	(215) 459-0390	
Waldman		662-3606	(267) 760-6477	
Wallack	308-0192	893-6200	(317) 997-1799	
Weinblatt	(610) 221-1412	662-4265	(610) 574-7889	Tamika Taylor
Willis		829-7915	(314) 704-9583	
Wolk		662-7810	(215) 219-1849	
Yuan		662-3376	(215) 908-0212	Justine Gallo

RESIDENT PHONE LIST – 2023-2024

Class	Resident	Work Cell	Personal Cell
SSARs	Berman, Sara E.	215-535-9815	845-642-1712
	Boylan, Kelly A.	215-535-9847	201-951-2714
	Brahmaroutu, Ankita V.	215-535-9845	512-983-8006
	Cort, Mark	215-535-9864	347-382-2926
	Fitts, Whitney	267-252-3026	267-304-6130
	Gambrah-Lyles, Claudia	267-253-1318	409-781-3697
	Harris, Nicholas		
	Kapoor-Heaphy, Bianca C.	267-254-8243	847-778-4667
	Keselman, Dennis	267-253-0690	
	Ljungberg, Lovisa	215-535-9886	617-529-0903
	Luna, Esteban	215-300-8224	724-972-2915
	McGarry, Laura M.	215-439-4297	732-693-8620
	Morganroth, Jennifer	215-535-9921	215-840-4966
	Onifade, Ogo-Oluwa O.	215-535-9929	443-466-7168
	Pappalardo, Laura W.	267-624-4221	512-826-6467
	Porcari, Giulia	215-586-0875	607-379-4392
	Rosenberg, Evan C.	215-535-9949	267-240-7128
	Sahu, Malya	215-535-9948	732-646-1001
	Silver, Maya	215-834-1232	781-996-9580
	Simoes-Jones, Felipe	215-301-7855	857-488-9982
	Venezia, Anya Grace	215-301-9332	339-237-2663
	Wadhwani, Anil	215-301-0467	815-919-8590
	Zuroff, Leah	215-535-9953	781-636-8031

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SARs	Agostinelli, Lindsay J.	215-327-3221	845-863-4020
	Bach, Ashley	267-588-1569	415-518-4175
	Boada, Christina M.	215-221-4320	412-953-5590
	Chang, Gina	267-441-9824	408-826-1011
	Elser, Holly C.	215-300-4361	267-322-0238
	Gentile, Caroline F.	215-554-0811	203-962-2817
	Han, Michelle	267-588-2295	319-541-1348
	Jenkins, Charmaine	267-588-1359	803-743-3144
	Kessler, Riley	267-588-1197	818-321-6922
	Little, Jessica N.	215-327-4107	910-920-6833
	Magee, Rogan G.	215-327-5684	636-226-8628
	Markwalter, Kelly	267-588-5572	703-945-2164
	Mestre Payne, Humberto	215-554-0747	914-208-6218
	Miller, Jenna L.	215-554-0617	504-616-3250
	Morrison, Andrew A.	215-554-1340	724-996-1148
	Perez, Michael A.	215-554-0721	305-903-6212
	Pisano, Thomas	267-588-4197	908-246-1731
	Xu, Linda B.	215-554-1512	615-877-4987
	Yousuf, Wajiha	215-554-1687	97450134023
	Zhou, Sonya E.	215-554-1675	203-889-7192
JARs	Belfar, Samuel	267-624-3216	732-406-9707
	Charsar, Brittany	267-624-3119	724-977-3741
	Chen, Alex	(215) 827-9554	678-392-5980
	Chioma, Vivian	(215) 776-7852	301-613-6888
	Cordisco, Anthony	(215) 600-9518	609-670-3936
	Cornblath, Eli	(215) 600-6263	734-474-9226
	Craddock, Kirsten	267-624-3244	203-524-6395
	Denison, Lydia	(267) 879-7237	770-656-3681
	Dravida, Swetha	267-624-3145	508-523-1837
	Eisinger, Robert	(267) 595-9428	407-234-1460
	Fonkeu, Yombe	(267) 595-7220	484-546-6223
	Gibson, Alec	(267) 595-8284	864-616-8744
	LaGrant, Brian	267-624-3425	315-534-4709
	Madu, Theandra	(267) 588-4953	804-914-0025
	Mivares-Hernandez, Laura		917-370-2914
	Ohanesian, Noelle	(215) 847-6498	518-956-1393
	Perkins, Jonathan	(267) 588-9334	412-715-2190
	Polott, Elizabeth (Libby)		216-544-0590
	Schneider, Sabine	(267) 591-8947	617-680-4341
	Shaik, Noor	(267) 592-8167	267-346-8070
	Zotter, Brendan	(267) 595-9521	703-966-4341

HUP DEPARTMENT OF NEUROLOGY PHONE LIST

Neurology Studies			
EEG	662-2661	Neuro Vasc Lab	662-3611
EEG Read Room	614-0194	VER/BAER	662-2663
EMG	662-2623	Visual Fields	662-2623
Neurology Pagers and Cell Phones		General Neurology Numbers	
Acute Stroke (Fellow/Attending)	349-5990	Neurology Appointment Line	662-3606

NOTES

Stroke Cell (Resident)	260-1959	Neurology Clinic	662-6565
Consult HUP	713-6506	Neurology Receptionist	662-2700
Epilepsy pager	404-6771	FAX: Neurology Department	349-5579
Neurovascular SAR	940-5331	Administration	662-3362
NICU Resident	906-2603		
NICU Fellow	275-2613		
NICU Attending	275-2617		
Pavilion 10 Pharmacist	459-2009		

PASSWORDS AND DOOR CODES

HUP
Ravdin 2 resident room 500677
3W Gates conference rooms: 500677
ED CT scanner: 62211
HUP MRI (ground Donner) control room: 088880

PAH
Long distance code: 68786
Call room Cathcart 748; code 51925
Ambulance Bay keypad: 0411#1
Consult Phone Code: 500677

PPMC
6th floor call room: go right off the elevator, door code 9714 □ first hallway on the left is the neuro room 7104#
PPMC office (Medical Office Building 3) 7141